Mediterranean Journal of Pharmacy & Pharmaceutical Sciences
www.medjpps.com ISSN: 2789-1895 online ISSN: 2958-3101 print

Review article

A progressive review on the synthesis of Atovaquone (an anti-malarial drug), empowered by the critical examination of prior-art disclosures

Sanjay Sukumar Saralaya [1 *] and **Shridhara Kanakamajalu** [2]
[1] Department of Chemistry, Sri Dharmasthala Manjunatheshwara Institute of Technology, Ujire, Karnataka, India
[2] Technical Coordinator, ArkGen Pharma Private Limited, Peenya Industrial area, Bangalore, Karnataka, India

[*]Author to whom correspondence should be addressed

Received: 12-11-2023, **Revised:** 25-11-2023, **Accepted:** 27-11-2023, **Published:** Preprint

HOW TO CITE THIS
Saralaya and Kanakamajalu (2023) A progressive review on the synthesis of Atovaquone (an anti-malarial drug), empowered by the critical examination of prior-art disclosures. Mediterr J Pharm Pharm Sci. 3 (4): 33-53. https://doi.org/10.5281/zenodo.10208022

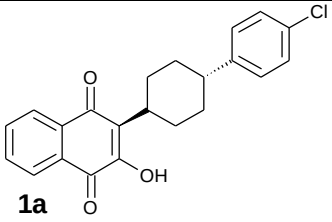
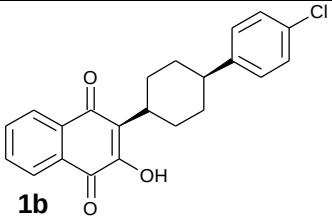
Keywords: Atovaquone, coupling, epimerization, hydrolysis, recrystallization, synthesis

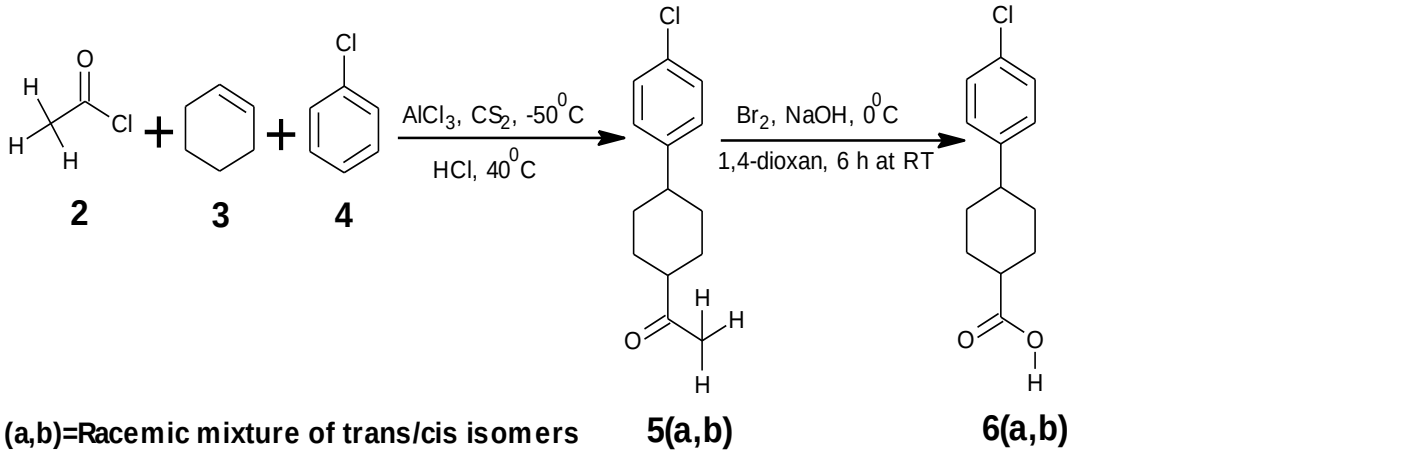
Abstract: In this article, a systematic flow of contents was provided with regard to the synthesis of Atovaquone **1a** on critical examination of the prior-arts. Several patents and study articles were published, disclosing different synthetic methods for the preparation of Atovaquone **1a** at various scales. Based on the starting materials used, there are a few one-step, two-step and multi-step synthetic routes were reported with varied yields. In this work, we have put in our sincere effort to collect all the synthetic routes of Atovaquone **1a** in detail with distinct and elaborate reaction schemes for a better and collective process clarity. From this review, global researchers will get a platform to re-design or re-work on the synthetic approach of Atovaquone **1a** with better atom economy and purity. In addition, the drug commercialization angle could also be looked in during the design stage itself alongside green chemistry concepts. We have done the chronic analysis of study articles to highlight the commercial feasibility of the disclosed synthetic methods. A special emphasis was given to the synthetic routes with process development initiatives towards, recovery/reuse of costly starting materials/reagents/solvents and their feasibility for large scale manufacturing of drug Atovaquone **1a**.

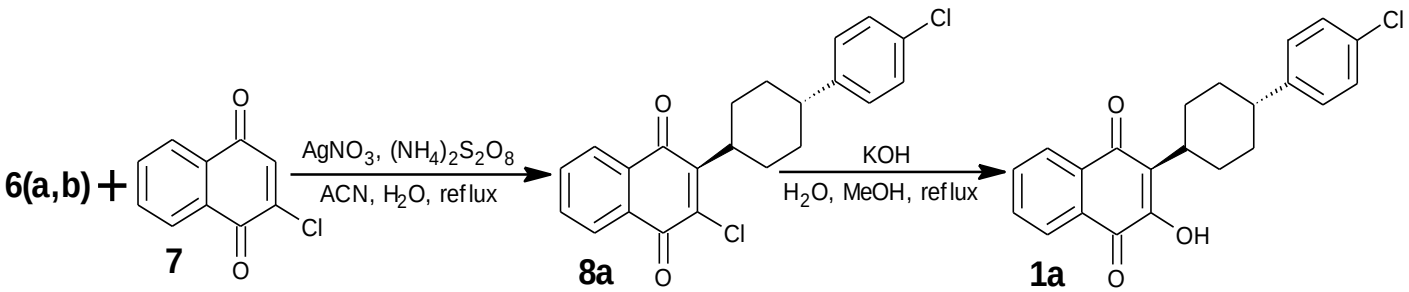
Introduction

Atovaquone (**1a**) is a popular anti-malarial drug, it belongs to the category of hydroxy-1,4-naphthoquinones. Some essential details of **1a** are tabulated in **Table 1**, to have its brief outline. Other popular drugs falling under the similar category are Parvaquone and Buparvaquone. It is proven to be effective for the treatment against Pneumocystis jirovecii pneumonia and Plasmodium falciparum malaria [1, 2]. It is administered with the drug Proguanil, for a better therapeutic efficacy [3-5]. It is popular even as an effective anti-cancer, anti-viral, anti-protozoal, anti-inflammatory and anti-fungal agent [6-12]. The poor water solubility of **1a**, had enforced to build a few of its prodrugs for a better bioavailability [13]. The synthesis of substituted 2-hydroxy-1,4-quinones had received considerable attention in medicinal chemistry over past few decades [14-16]. The drug under focus **1a**, has the hydroxyl (-OH) group attached to the naphthaquinone ring at position-2 and the substituted cyclohexyl group attached to the position-3. Several patents and study articles were reviewed in detail for the disclosed synthetic strategies of **1a** with elaborate reaction schemes.

Table 1: Basic details about the drug, **1a**

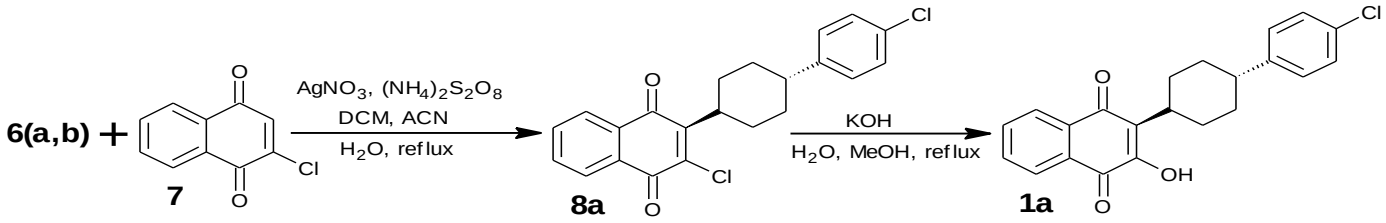
Category	**Details**
Generic name	Atovaquone
Class	Naphthoquinones
Analogue of	Ubiquinone and Lawsone
Pharmacological activity	Anti-microbial
Brand/Trade name	Mepron, Malarone
Molecular formula	$C_{22}H_{19}ClO_3$
Molecular weight	366.84
Melting point (m.p.)	216 - 219 ^oC
IUPAC name	*trans*-2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione
CAS registry number	95233-18-4
Drug bank accession number	DB01117
FDA approval	1999
Chemical structure of the drug, *trans*-Atovaquone	 **1a**
Chemical structure of *cis*-Atovaquone	 **1b**



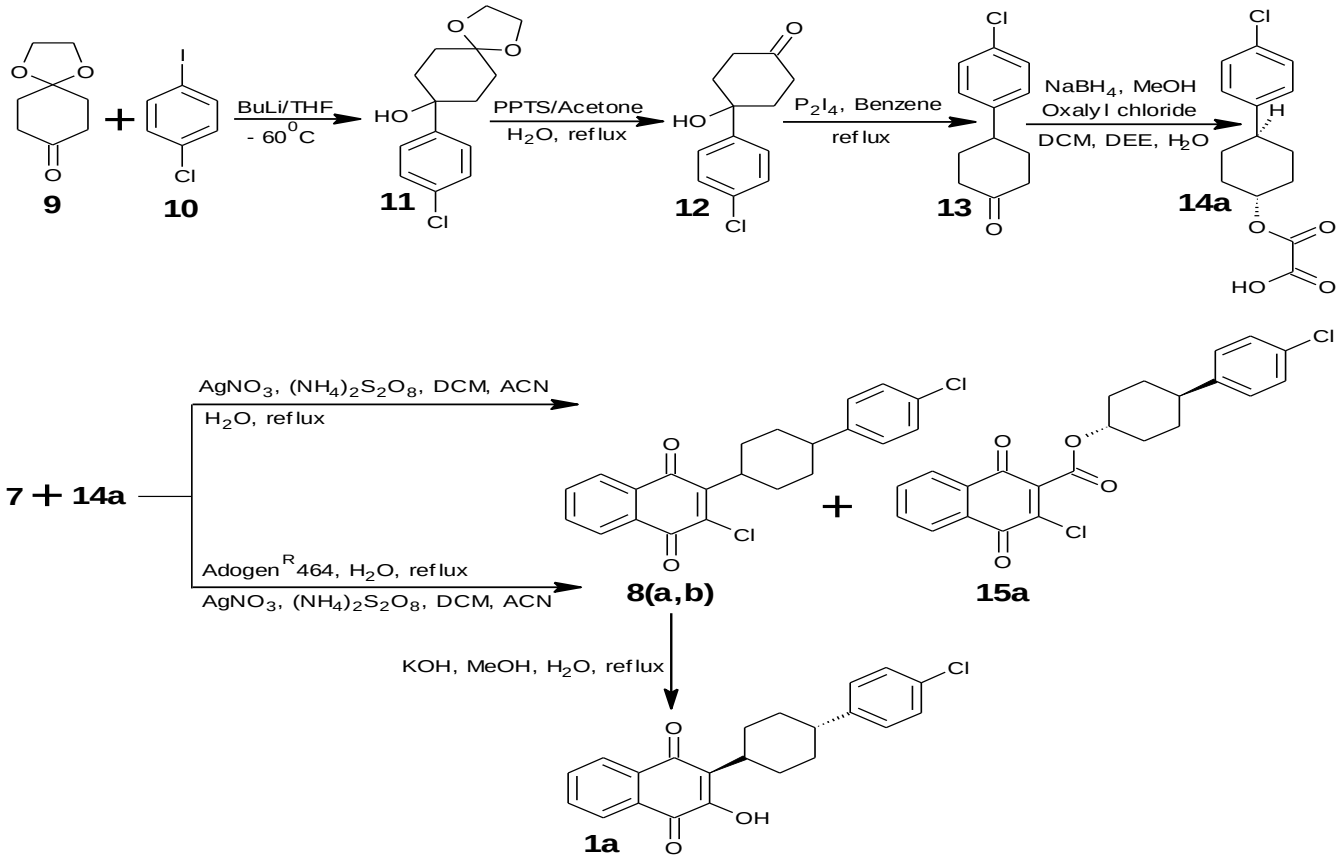


Scheme 1: Synthesis of **1a** from **2**, **3**, **4** and **7**

In 1989, Hudson et al. [17, 18] had reported the reaction of acetylchloride **2** and cyclohexene **3** at a low temperature in the presence of anhydrous aluminum chloride ($AlCl_3$) using carbon disulphide (CS_2). To the reaction mixture, added chlorobenzene **4** (as the reagent and solvent) at a room temperature and maintained at 40°C for 3 hr. It was quenched to cold hydrochloric acid (HCl) and the organic layer was retained for the acid wash, alkali wash, water wash, and solvent evaporation. The oily mass has finally been subjected to fractional distillation to obtain 1-[4-(4-chlorophenyl)cyclohexyl]ethanone **5**(**a**,**b**). The fraction boiling at 140-154°C, which was enforced out under the reduced pressure of 0.1 mm Hg was collected as **5**(**a**,**b**). Bromine (Br_2) in alkaline medium was reacted with **5**(**a**,**b**) in 1,4-dioxan for 6 hr., later acidified, filtered, washed, dried and recrystallized from ethanol to get 4-(4-chlorophenyl)cyclohexane-carboxylic acid **6**(**a**,**b**) with a m.p. of 254-256°C. 2-Chloro-naphthalene-1,4-dione **7** and **6**(**a**,**b**) were coupled under the joint mediation of finely powdered silver nitrate ($AgNO_3$) and ammonium persulfate {$(NH_4)_2S_2O_8$} in acetonitrile and water under reflux, to get 2-chloro-3-[*trans*-4-(4-chlorophenyl)cyclohexyl]n-aphthalene-1,4-dione **8a** with a m.p. of 172-175°C. Hydrolysis of **8a** using potassium hydroxide (KOH) in aqueous alcohol, followed by acidification, filtration and recrystallization from acetonitrile gave **1a** with a m.p. of 216-219°C (yield: 3.98%, as from **7**), (**Scheme 1**). Due to poor yield, the disclosed process does not suite economically for the large scale manufacturing of the drug.

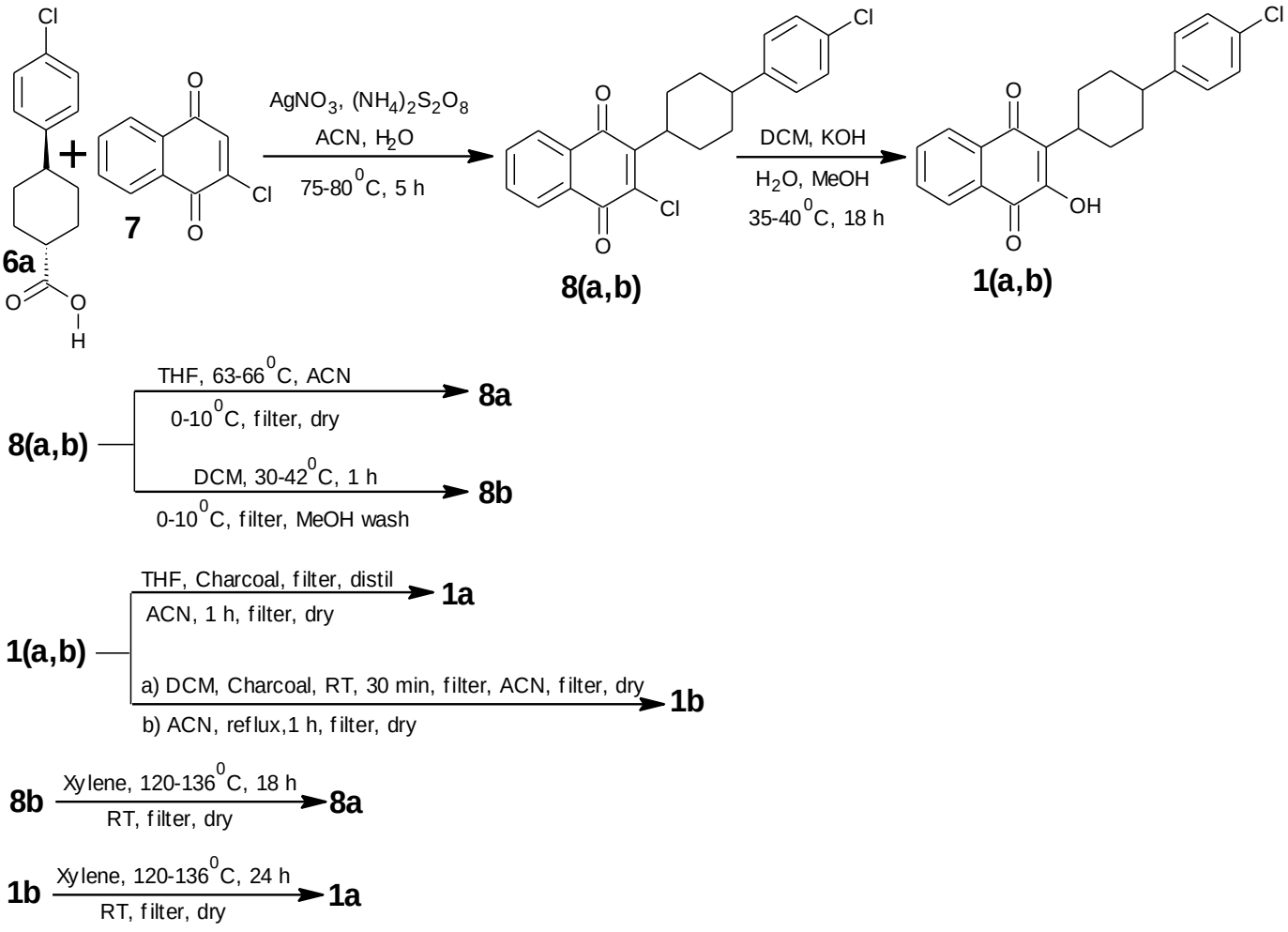


Scheme 2a: Synthesis of **1a** from **6**(**a**,**b**) and **7**



Scheme 2b: Synthesis of **1a** from **7**, **9, 10** and **14a**.

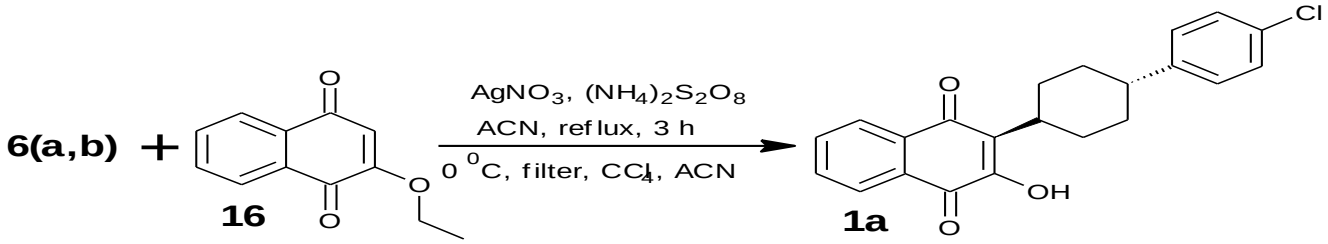
Inspired by the initiatives of Coppa et al. [19], in 1998, Williams et al. [20] had demonstrated the condensation of **6**(**a**,**b**) and **7** under the catalytic influence of $AgNO_3$ in the presence of $(NH_4)_2S_2O_8$ using a bi-phase solvent system comprising dichloromethane and aqueous acetonitrile to get **8a** (yield: 14%). Hydrolysis of it by KOH solution in methanol, followed by acidification and recrystallization from hot acetonitrile gave **1a** (yield: 14.01%, as from **7**). Substantial yield improvement was observed by the use of aqueous bi-phase solvent system for the process (**Scheme 2a**). Further, 1,4-dioxaspiro[4.5]decan-8-one **9** and 1-chloro-4-iodobenzene **10** have been reacted in the presence of butyl-lithium (BuLi) in tetrahydrofuran (THF) at -60°C to get 8-(4-chloro-phenyl)-1,4-dioxaspiro[4.5]decan-8-ol **11**. Hydro-lysis of it using pyridinium-*para*-toluene sulfonate (PPTS) and aqueous acetone gave **12**. Diphosphoroustetraiodide (P_2I_4) mediated de-oxygenation of **12** in benezene had led to the formation of 4-(4-chlorophenyl)cyclohexanone **13**. It was subjected to reduction using sodium borohydride ($NaBH_4$) in methanol, followed by acylation using oxalyl chloride in dichloromethane and water quench gave {[*trans*-4-(4-chlorophenyl)cyclo-hexyl]oxy}(oxo)acetic acid **14a** (yield: 65%, as from **9**). **7** and **14a** were reacted under the above said bi-phase solvent system to get the mixture of **8**(**a**,**b**) (yield: 5%) along with *trans*-4-(4-chloro-phenyl)cyclohexyl 3-chloro-1,4-dioxo-1,4-dihydr-onaphthalene-2-carboxylate **15a** (yield: 15.0%). Introduction of a phase transfer catalyst (Adogen®464) for the above reaction had shown drastic raise in the conversion rate to generate the mixture of **8**(**a**,**b**) (yield: 43.0%) along with **15a** (yield: 38%). Interestingly, the reaction of **7** and **14a** under silver nitrate mediation in the presence of $(NH_4)_2S_2O_8$ using acetonitrile had failed to go for the conversion, to form either **8**(**a**,**b**) or **15a** (**Scheme 2b**). The multi-step pathway, relatively low yield and the formation of isomeric mixtures had made this process to be fine-tuned further to suite for a large scale manufacturing of the drug.



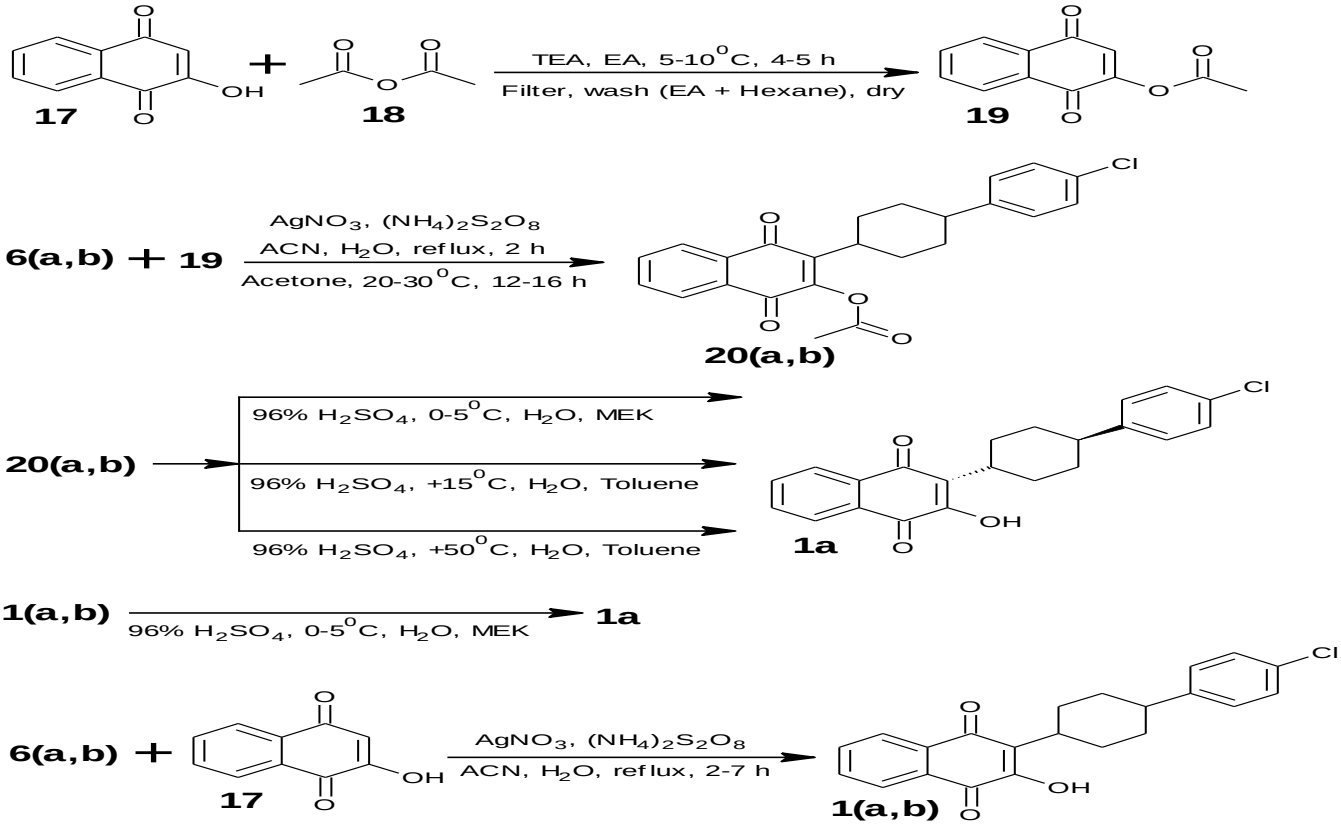
Scheme 3: Synthesis of **1a** from **6a** and **7**

In 2008, Verma et al. [21] had illustrated the $AgNO_3$ and $(NH_4)_2S_2O_8$ mediated condensation of **6a** and **7** in acetonitrile and water at 75-80°C for 5-6 hr, followed by distillation, cooling, water wash and drying to get **8**(**a**,**b**) (yield: 47.0%). Dichloromethane was added to the mixture, stirred at RT for 1.0 hr and filtered. The filtrate obtained was directly taken up for alkali (KOH) mediated hydrolysis in aqueous methanol at 35-40°C for 18-20 hr. Post reaction completion, added HCl to adjust the acidity to pH: 2 before the filtration to get **1**(**a**,**b**) (yield: 67%). It was subjected to charcoal treatment in THF, followed by solvent evaporation, acetonitrile addition and filtration to get **1a** (yield: 22-23%, as from **8**). In addition, work emphasizes on the solvent/temperature mediated inter-conversion of racemic mixtures (intermediate or crude final product) to their respective pure isomeric forms (**Scheme 3**). This process was executed in a substantial high scale with moderate yield, thus gains the feasibility for large scale manufacturing with isomeric inter-conversion capability.

In 2008, Wang et al. [22] had reported the condensation of **6**(**a**,**b**) with 2-ethoxynaphthalene-1,4-dione **16** in the presence of $AgNO_3$ by the varied input of $(NH_4)_2S_2O_8$ in aqueous acetonitrile medium under reflux for 3-4 hr gave **1**(**a**,**b**). The reaction mixture was cooled to RT, added carbon tetrachloride and filtered to remove the insolubles. Furthermore, the solvent evaporation and recrystallization from acetonitrile gave **1a** with a m.p. of 216-219°C (yield: 7-8%, as from **16**). This process (**Scheme 4**) could effectively be taken up for large scale manufacturing, since it is a feasible one-step process with a moderate yield.

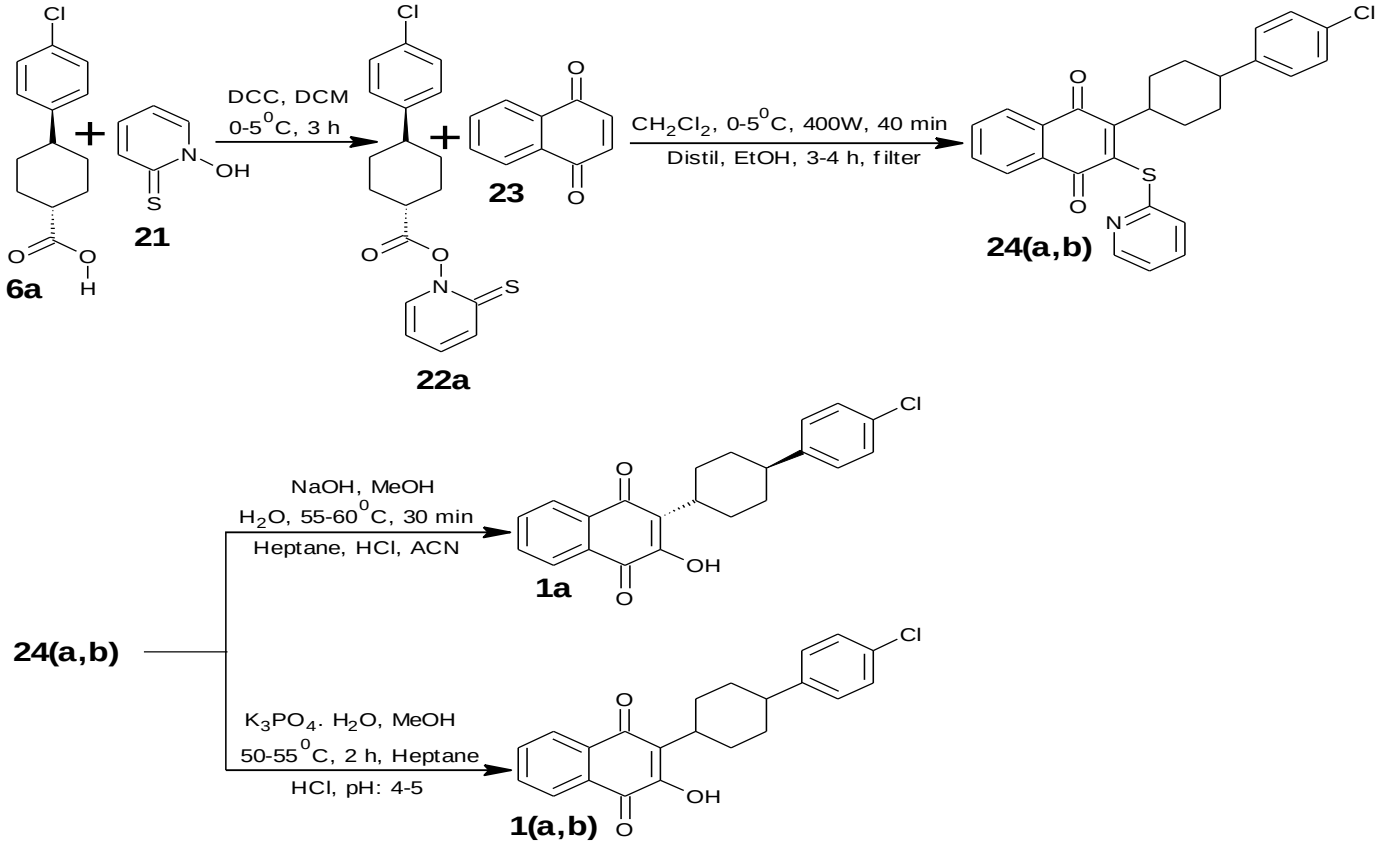


Scheme 4: Synthesis of **1a** from **6 (a,b)** and **16**



Scheme 5: Synthesis of **1a** from **6** (**a**,**b**) from **17** and **18**

In 2008, Antonio et al. [23] had demonstrated the acylation of 2-hydroxynaphthalene-1,4-dione **17** by acetic anhydride **18** under the mediation of triethylamine (TEA) in ethyl acetate at 05-10°C for 4-6 hr to get 1,4-dioxo-1,4-dihydronaphthalen-2-yl acetate **19** (yield: 80%). The condensation of **6**(**a**,**b**) and **19** was done in the catalytic presence of $AgNO_3$ using $(NH_4)_2S_2O_8$ in acetonitrile and water for 2-3 hr, followed by the sequential steps like toluene addition, phase separation, sodium chloride (NaCl) solution wash, water wash, distillation, cooling, filtration, drying and the parallel product isolation from the filtrate gave **20**(**a**,**b**) (yield: 41.7%). The solid isolated by direct filtration gave **20b** (Ist crop-major) with a m.p. of 197-200°C and the solid isolated from the filtrate had **20a** (IInd crop-minor) with a m.p. of 150-155°C. The epimerization and de-protection of **20**(**a**,**b**) was done by using concentrated sulfuric acid (H_2SO_4) at different temperature. At 0-5°C for 30 min, water quenching and the use of methyl ethyl ketone (MEK) gave **1a** (yield: 67.0%) with a m.p. of 220-223°C. A similar pathway at +15°C and the use of toluene instead of MEK, gave **1a** (yield: 76%). Furthermore, a similar attempt at 50°C, gave **1a** (yield: 25.0%). An isomeric mixture of **1**(**a**,**b**), having 58.0% of **1b** and 48.0% of **1a** was subjected to concentrated H_2SO_4 treatment at 5°C, followed by water quenching and MEK influenced isolation gave **1a** (yield: 81.0%). An attempt has also been done to condense **17** with **6**(**a**,**b**) under silver and persulfate mediated pathway to achieve a below par conversion rate of only 10.0% (**Scheme 5**). A large volume of solvent utility and isomer separation issues are key factors which forms a setback for the scalability of the disclosed synthetic pathway.

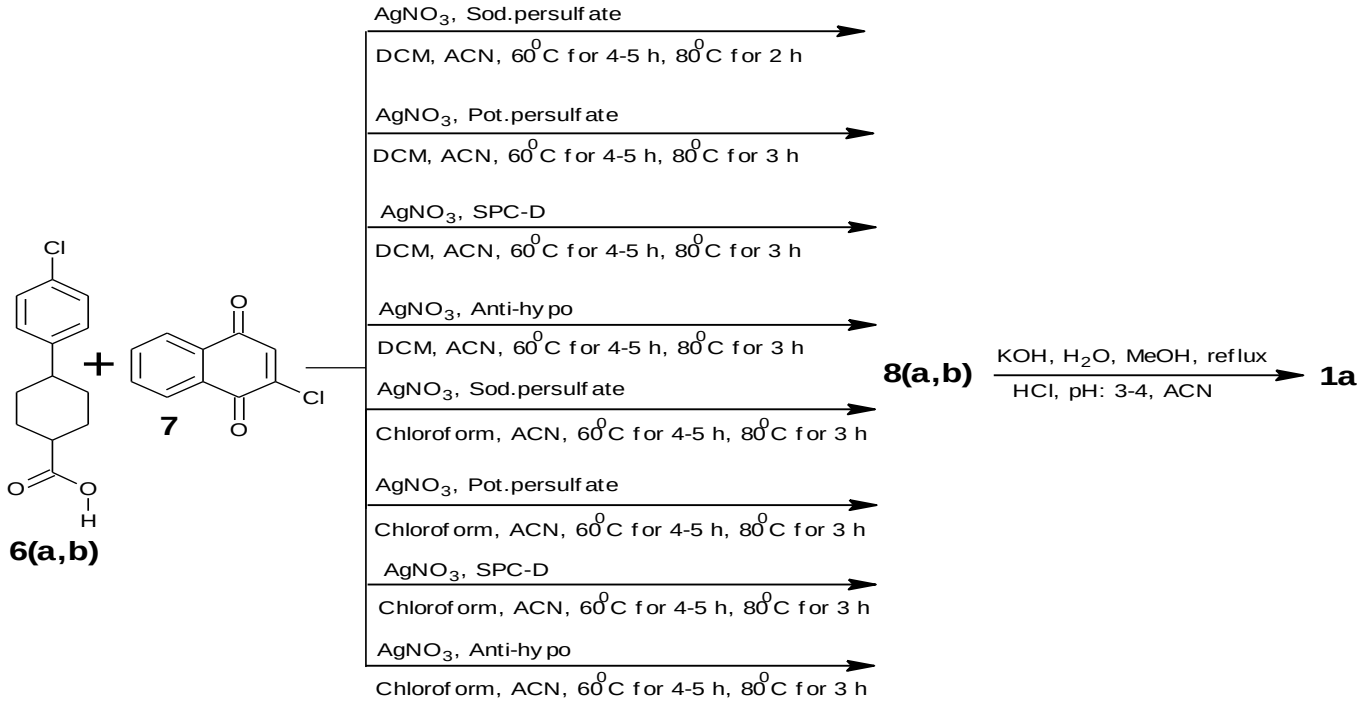


Scheme 6: Synthesis of **1a** from **6a**, **21** and **23**.

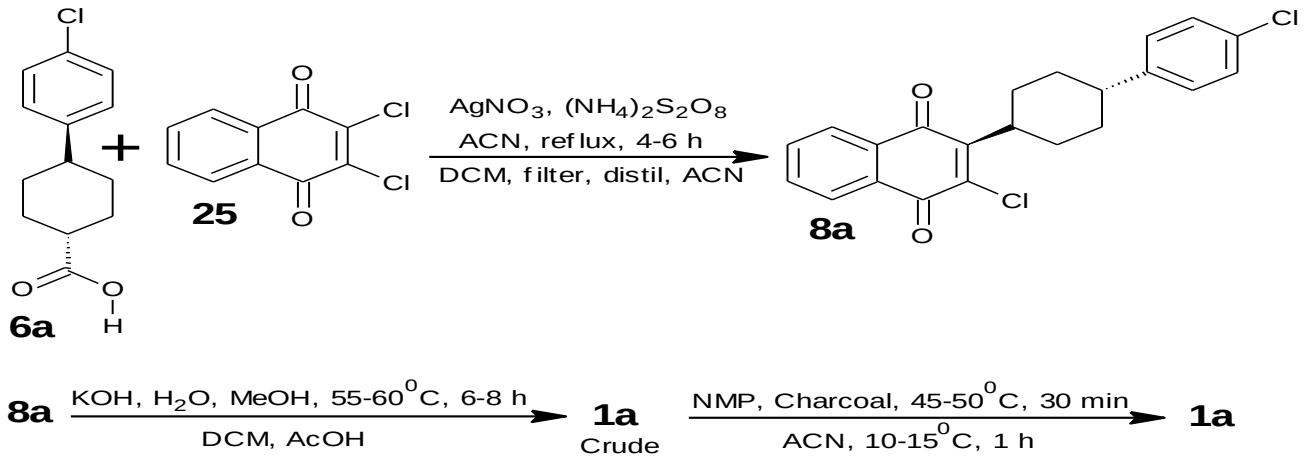
In 2008, Zhu et al. [24] had reported the coupling of *N*-hydroxypyridine-2-thione **21** with **6a** under the catalytic mediation of dicyclohexylcarbo-diimide (DCC) in dichloromethane at 0-5°C for 2 hr to isolate *trans*-2-thioxopyridin-1 (2*H*)-yl-4-(4-chlor-ophenyl)-cyclohexane carboxylate **22a** (yield: 87.8%) with a m.p. of 153-156°C. It was condensed with naphthalene-1,4-dione **23** in dichloromethane at 0-5°C under the irradiation of 400W halogen lamp for 40 min, followed by distillation and ethanol slurry gave 2-[4-(4-chloro-phenyl)cycloh-exyl]-3-(2-pyridin-2-yl-thio)-naph-thalene-l,4dione **24**(**a**,**b**) (yield: 80.2%), comprising 48.0% of **24b** and 38% of **24a**. Purifi-

cation of **24**(**a**,**b**) was done by the use of various solvents through slurry wash or recrystallization techniques to get the isomeric purity in the range of 92-96% with a recovery of 50-85%. Hydrolysis of **24**(**a**,**b**) using sodium hydroxide (NaOH) in aqueous methanol at 55-60^{o}C for 30 min, followed by n-heptane addition, acidification and recrystallization from acetonitrile gave **1a** (yield: 12.0%) with 99.35% of purity. Similarly, hydrolysis of **24**(**a**,**b**) using tri-potassium phos-phatetrihydrate (K_3PO_4. $3H_2O$) in aqueous methanol at 50-55^{o}C for 2 hr, followed by n-heptane addition and acidification to pH 4-5 gave **1**(**a**,**b**) (80.0% yield), comprising 48.0% of **1b** and 41.5% of **1a** (**Scheme 6**). The process successfully avoids the use of expensive reagent silver nitrate, thus becomes commercially viable for scalability.

In 2009, Gui et al. [25] had illustrated the condensation of **6**(**a**,**b**) with **7** under the catalytic presence of $AgNO_3$ in an aqueous bi-phase solvent system with the use of different oxidizers to get **8**(**a**,**b**), its hydrolysis, acidification and crystallization in acetonitrile gave **1a** (yield: 24-35%, as per **7**). Along-with acetonitrile, dichloromethane or chloroform was used for the reaction and four different oxidizing agents were used in distinct experiments (**Scheme 7**) to get **8**(**a**,**b**) and later **1a** with the purity of around 98.2-99.3%. This two-step process provides a moderate yield with good purity, it will suite for a large scale manufacturing.

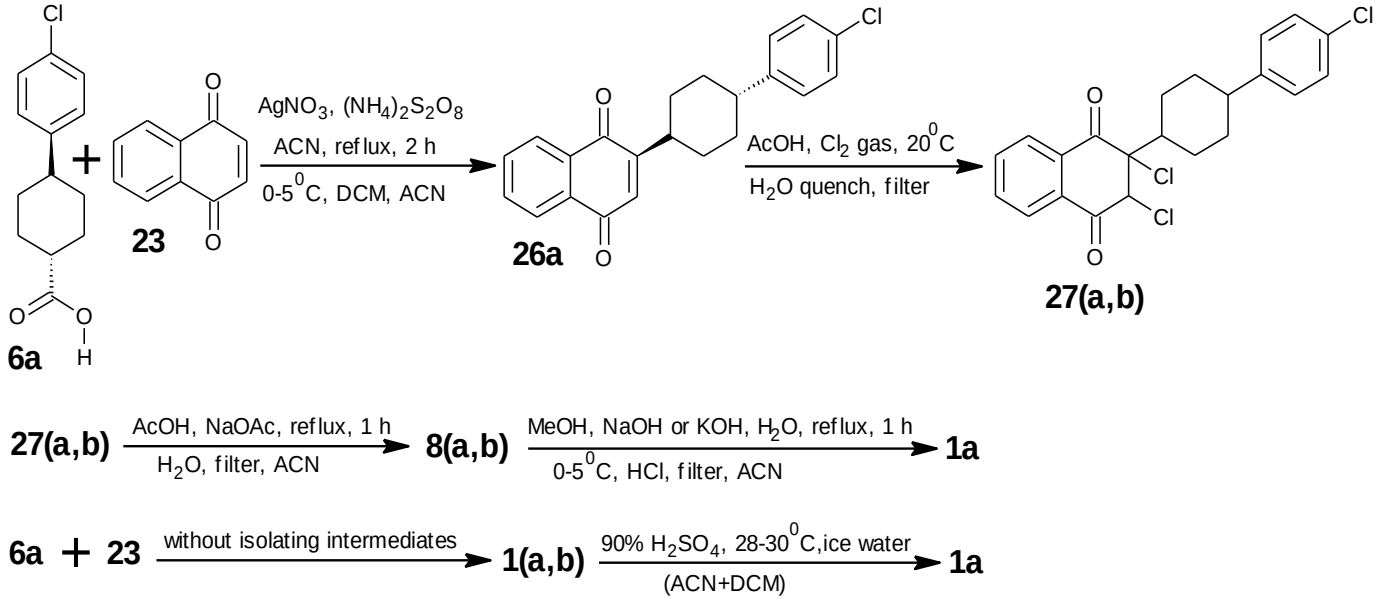


Scheme 7: Synthesis of **1a** by the condensation of **6**(**a**,**b**) and **7**.



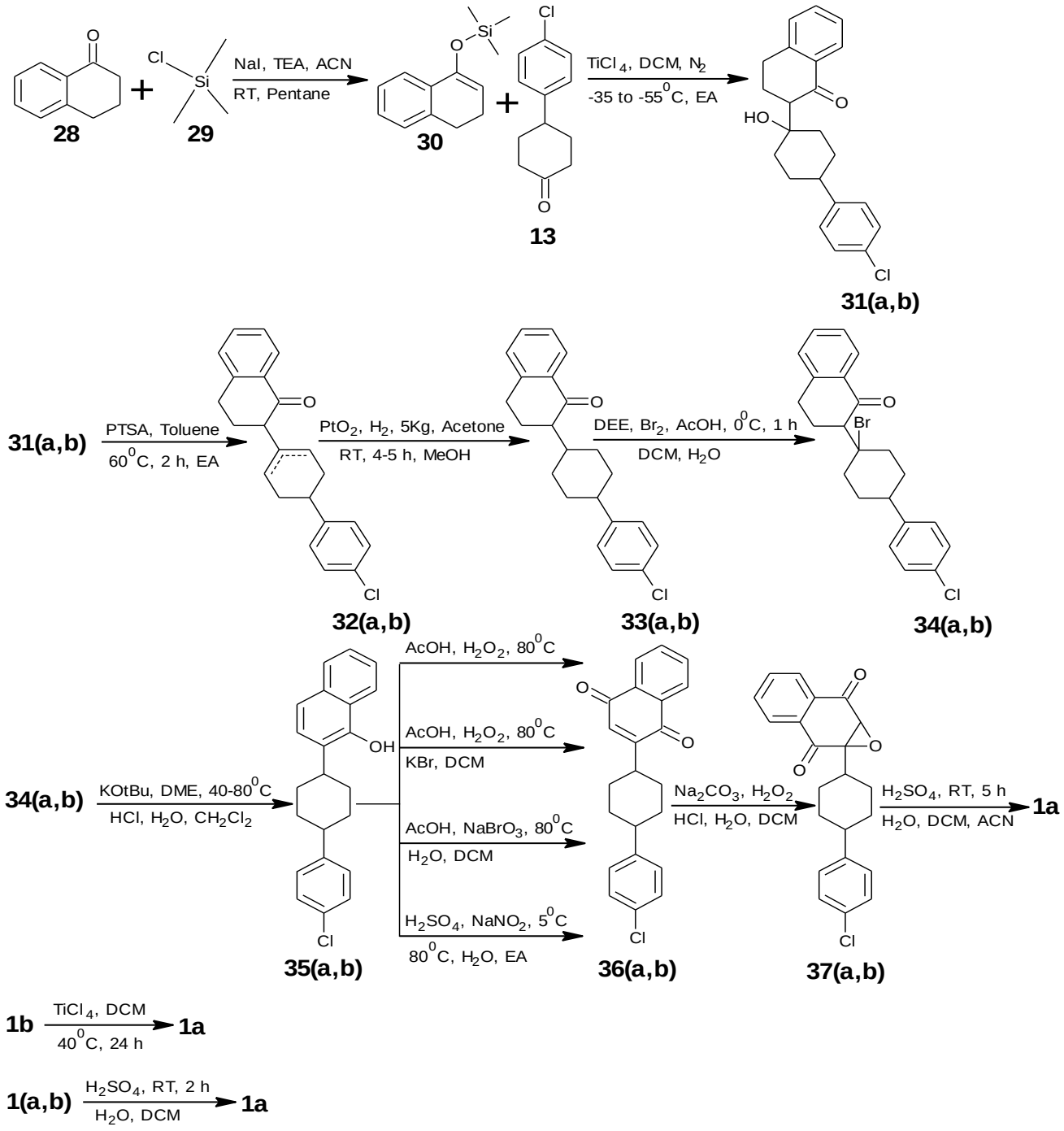
Scheme 8: Synthesis of **1a** from **6**(**a**,**b**) and **25**.

The past disclosed method was refurbished in 2009/2022 by Saralaya et al. [26-28] to condense **6a** with 2,3-dichloronaphthalene-1,4-dione **25** under the influence of $AgNO_3$ and $(NH_4)_2S_2O_8$ in aqueous acetonitrile under reflux for 4-6 hr to get **8a** (yield: 40-42%). A significant process optimization studies were conducted to achieve better atom economy and good purity. The recovery and reuse of expensive silver salt was achieved along with solvents such as acetonitrile and dichloromethane. The hydrolysis of **8a** was done using KOH solution in methanol under reflux for 4-6 hr. To the dark red reaction mass at RT, dichloromethane was added, acidified by acetic acid (AcOH), filtered and crystallization was done by the solvent mixture (acetonitrile and *N*-methyl pyrrolidone) to isolate **1a** (yield: 90-95%). Hydrolysis and recrystallization steps were optimized to achieve the reduction in alkali addition, acidifier acid selection, and use of solvent combination in reduced volume for the crystallization of crude **1a** to get better yield and purity (**Scheme 8**). This process involves the use of abundant and cheaper raw material **25** giving the best output in terms of product yield and purity. The process was empowered with recovery and reuse studies, it avoids column chromatography for the product isolation and involves an optimized input of solvents and reagents. The process fits well for the large scale manufacturing of the drug.

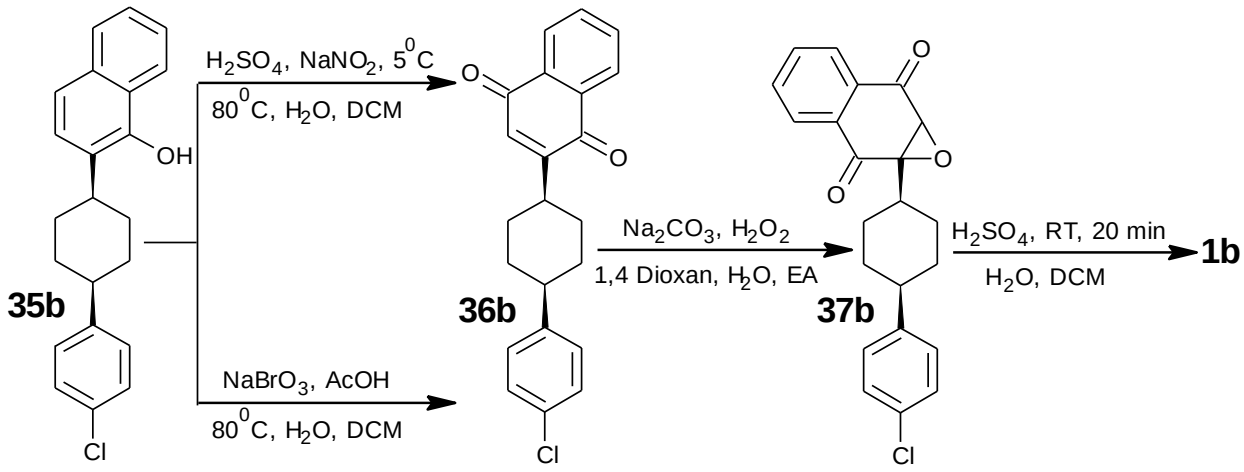


Scheme 9: Synthesis of **1a** from **6a** and **23**

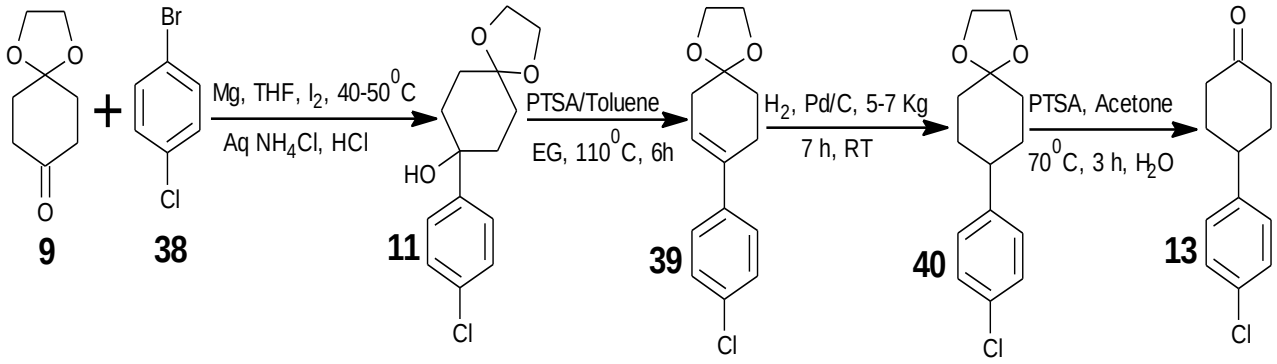
In 2009, Kumar and others [29] had disclosed the silver and persulfate driven reaction pathway to condense **6a** and **23** in acetonitrile and water medium under reflux for 2 hr to get 2-[*trans*-4-(4-chlorophenyl)cyclohexyl]naphthalene-1,4-dione **26a** (yield: 20.0%) with a m.p. of 146-149°C (as recrystallized from acetonitrile). Chlorine gas (Cl_2) was passed to **26a** in glacial AcOH at 20°C and later quenched to water to get 2,3-dichloro-2-[4-(4-chlorophenyl)cyclohexyl]-2,3-dihydronaphthalene -1,4-dione **27**(**a**,**b**) (yield: 95.0%). It has then been taken in glacial acetic acid and refluxed with anhydrous sodium acetate (NaOAc) for 1 hr, followed by recrystallization in acetonitrile to isolate **8**(**a**,**b**) (yield: 70%). An alkali (NaOH or KOH) driven hydrolysis of **8**(**a**,**b**) in aqueous methanol under reflux, followed by acidification and acetonitrile recrystallization gave **1a** (yield: 70-86%). A similar process pathway (**Scheme 9**) was followed and the intermediates were not isolated to get **1**(**a**,**b**). Further, its epimerization by 90% H_2SO_4 at 28-30°C and recrystallization by the solvent mixture (acetonitrile & dichloromethane) gave **1a** (yield: 28.5%) with a purity of 99.8%. The disclosed process was empowered with an acid mediated epimerization pathway and a solvent driven recrystallization technique to isolate the intermediates and the product in good yield and purity. Hence, the process will suite for the large scale manufacturing of the drug.



Scheme 10a: Synthesis of **1a** from **13**, **28** and **29**



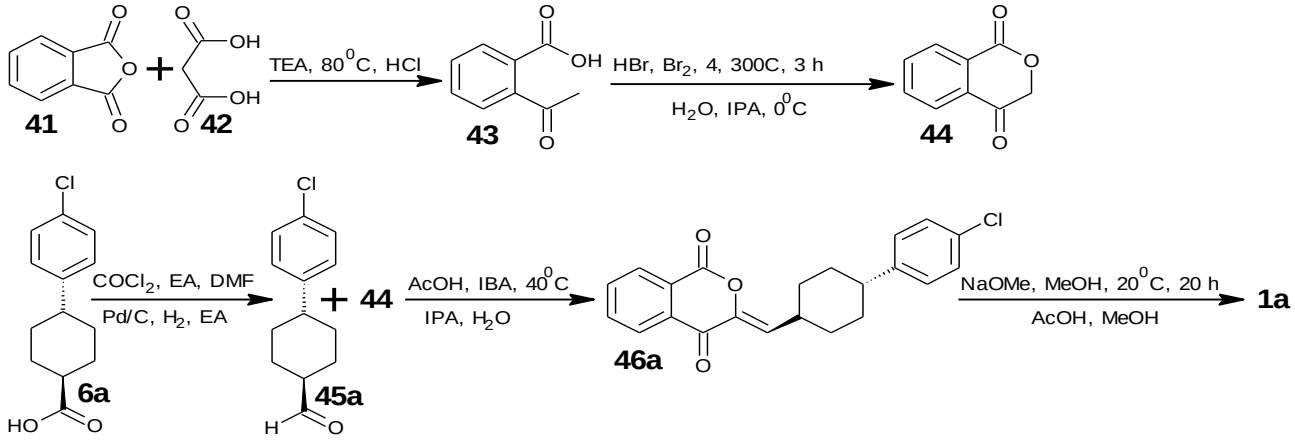
Scheme 10b: Synthesis of **1b** from **35b**.



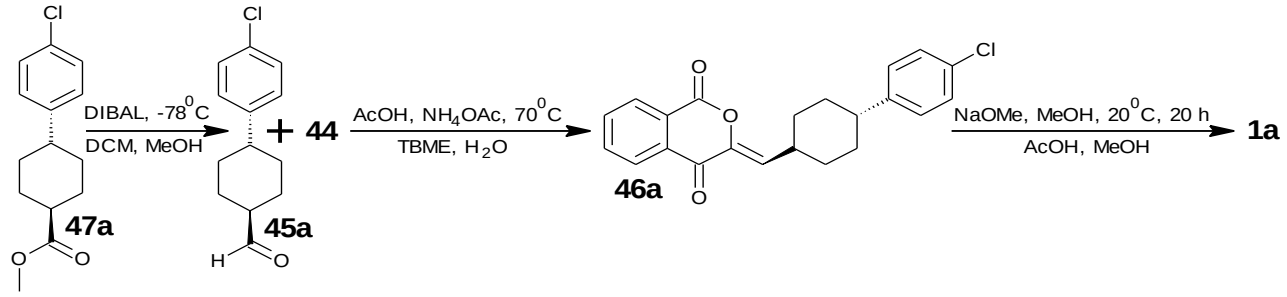
Scheme 10c: Synthesis of **13** from **9** and **38**

In 2011, Roy et al. [30] had demonstrated the condensation of 3,4-dihydronaphthalen-1(2*H*)-one **28** and trimethylsilyl chloride **29** in the presence of triethylamine (TEA) and sodium iodide (NaI) in acetonitrile, followed by quenching to water and n-pentane extraction gave (1, 2-dihydronaphthalen-4-yloxy)trimethylsilane **30** (yield: 90-97%). The reaction of **13** and **30** under the catalytic influence of titanium tetrachloride ($TiCl_4$) in dichloro-methane at -55°C, followed by quenching to ice water, bicarbonate wash, ethyl acetate slurry and filtration gave 2-[4-(4-chlorophenyl)-1-hydroxy-cyclohexy-l]-3,4-dihydronaphthalen-1(2*H*)-one **31**(**a**,**b**) (78-85%). It was treated with *para*-tolune sulfonic acid (PTSA) in toluene at 60°C for 2 hr, followed by the addition of ethyl acetate, bicarbonate wash, brine wash, solvent evaporation and recrystallization in methanol gave 2-(4-(4-chlorophenyl) cyclohex-l-enyl)-3,4-dihydrona-phthalen-l 2H)-one **32**(**a**,**b**) (yield: 45-56%). Its reduction under the catalytic influence of platinum oxide (PtO_2) in autoclave, followed by spent catalyst filtration, solvent evaporation and methanol recrystallization gave 2-[4-(4-chloro-phenyl)cyclohexyl]-3,4-dihydronaphthalen-1(2*H*)-one **33**(**a**,**b**) (yield: 85-95%). Its bromination by Br_2 in diethyl ether (DEE) and AcOH at 0°C, followed by dichloromethane addition, water wash, 5% sodium thiosulphate solution wash and solvent evaporation had led to the isolation of 2-[1-bromo-4-(4-chlorophenyl)cyclohexyl]-3,4-dihydronaph-thalen-1(2*H*)-one **34**(**a**,**b**) (yield: 95-99%). The influence of potassium *tert*-butoxide (KOtBu) in dimethoxy ethane (DME) on **34**(**a**,**b**), followed by the addition of 10% aqueous HCl, dichloromethane extraction and solvent evaporation gave 2-[4-(4-chlorophenyl)cyclohex-yl]naphthalen-1-ol **35**(**a**,**b**) (yield: 70-80%). It was converted to 2-[4-(4-chlorophenyl)cyclo-hexyl]naphthalene-1,4-dione **36**(**a**,**b**) (yield: 32-70%) by the use of four different reagents with varied outputs. The reagents used are hydrogen peroxide (H_2O_2) in AcOH (yield: 32%), H_2O_2 and potassium bromide (KBr) in AcOH (yield: 50%), sodium bromate ($NaBrO_3$) in AcOH (yield: 66%) and sodium nitrite ($NaNO_2$) in H_2SO_4 (yield: 70.0%). In above experiments isolation of **36**(**a**,**b**) was done by column chromatography using eluents with suitable polarity. The impact of sodium carbonate (Na_2CO_3) and hydrogen peroxide (H_2O_2) in 1,4-dioxan on **36**(**a**,**b**), ethyl acetate extraction and solvent evaporation gave 1a-[4-(4-chloro-phenyl)cyclohexyl]-1a,7a-dihydrona-phtho[2,3-*b*]oxirene-2,7-dione **37**(**a**,**b**). Its exposure to H_2SO_4 at RT, followed by dichloro-methane extraction, solvent evaporation and recystallization from acetonitrile gave **1a** (yield: 74.0%). Present work had given a method for the conversion of **1b** to **1a** under $TiCl_4$ mediation at 40°C for 24 hr (**Scheme 10a**). **35b** was converted to **36b** under $NaNO_2$ mediation or by $NaBrO_3$ mediation (yield: 55-65%). It was reacted with Na_2CO_3 and H_2O_2 in 1,4-dioxan had led to the formation of **37b** (yield: 90%). It was exposed to H_2SO_4, followed by water quenching, dichloro-methane extraction and distillation gave **1b** (**Scheme 10b**). Magnesium turnings and iodine (I_2) mediated reaction to couple **9** and 1-bromo-4-chlorobenzene **38** in THF at 40-50°C, followed by quenching to NH_4Cl solution, acid treatment and filtration gave **11** (yield: 93%). It has been treated with PTSA in toluene and ethylene glycol (EG) at 110°C for 6.0 hr, followed by solvent evaporation, 1.0% bicarbonate slurry

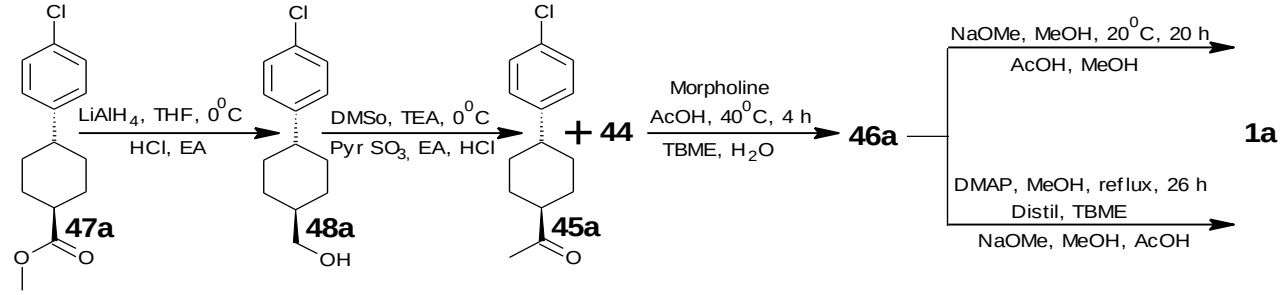
wash and filtration gave 8-(4-chlorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene **39** (yield: 90-97%). Its reduction by palladium/carbon (Pd/C) in autoclave with H_2 pressure of 5-7 Kg/cm^2 gave **40**, it was treated with PTSA in acetone at 70^{o}C for 3 hr, followed by acetone evaporation, sodium carbonate slurry wash and filtration gave **13** (yield: 80-90%) (**Scheme 10c**), the disclosed multi-step process has moderate yield, column chromatography based isolation and the formation of racemic intermediates/product. These parameters would form a certain bottle neck for the industrial production of the drug.



Scheme 11a. Synthesis of **1a** from **6a**, **41** and **42**



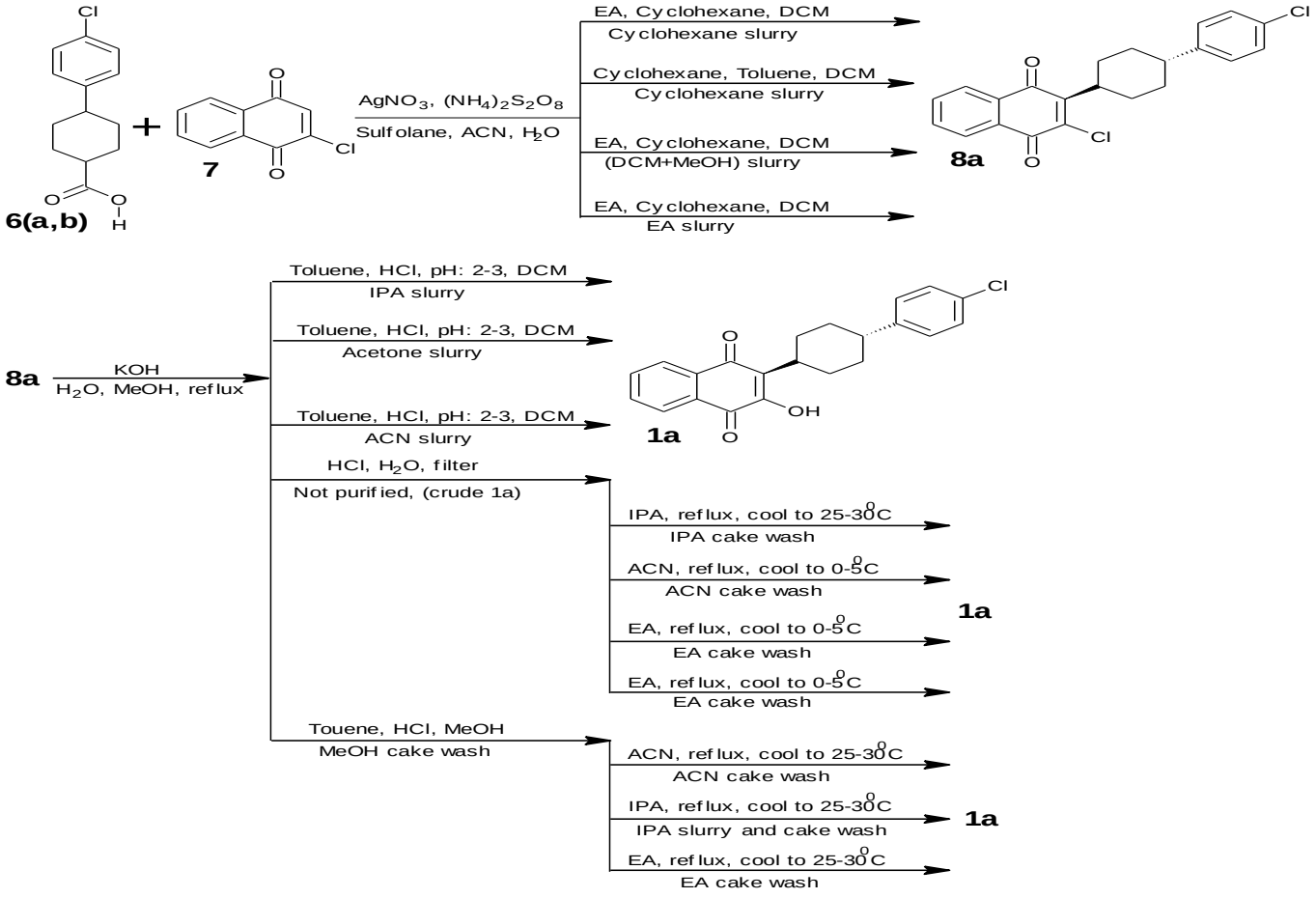
Scheme 11b. Synthesis of **1a** from **44** and **47a**.



Scheme 11c. Synthesis of **1a** from **44** and **47a**

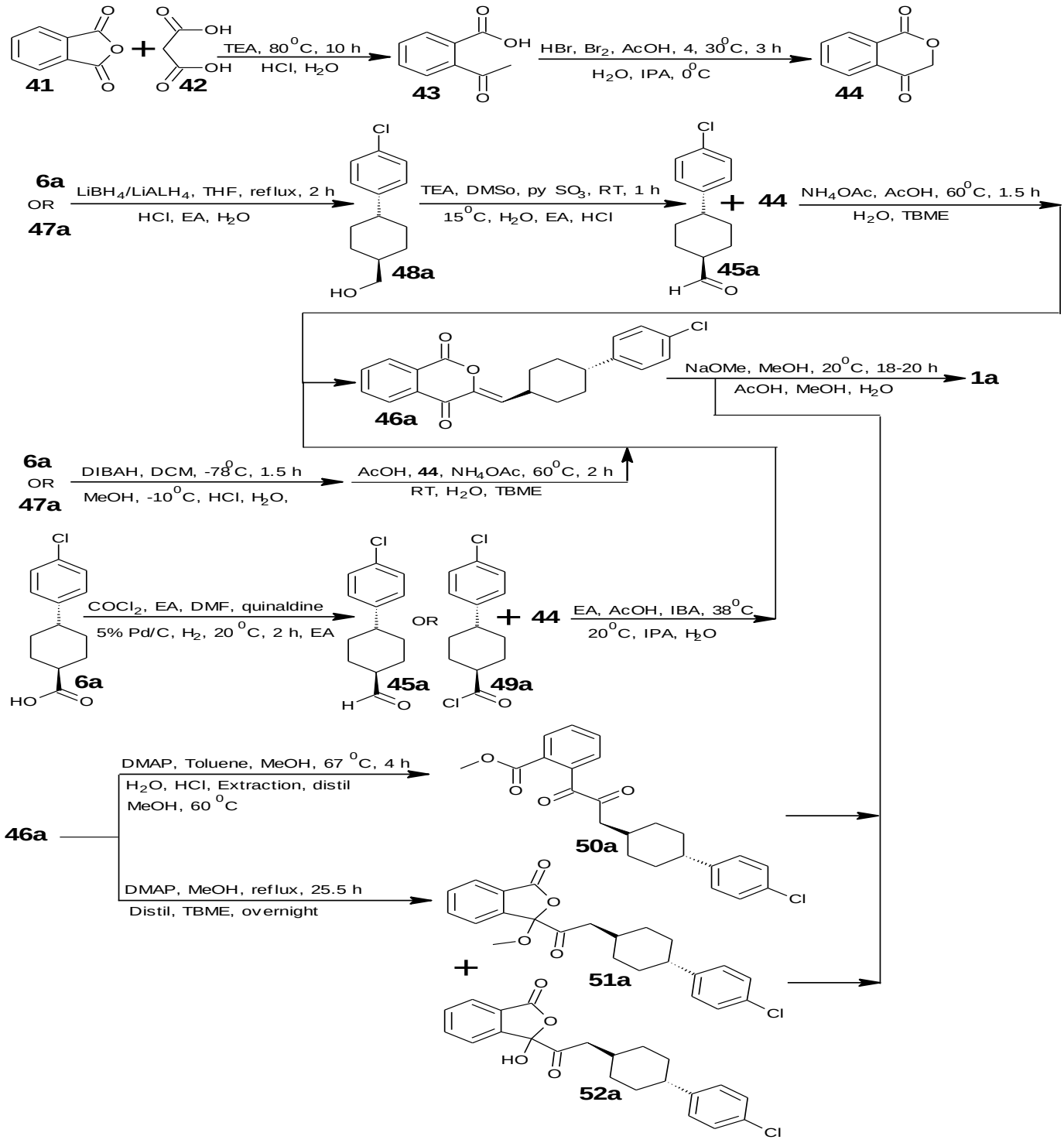
In 2011, Dwyer et al. [31] had reported the reaction of phthalic anhydride **41** and malonic acid **18** in the presence of TEA at 80^{o}C, followed by acid (HCl) quench and filtration to get 2-acetyl benzoic acid **43** (yield: 68.0%). The solution of **43** in chlorobenzene **4** (as solvent) was treated with hydrobromic acid (HBr) in AcOH and Br_2, followed by slow addition of water extraction, solvent extraction, solvent evaporation, isopropyl alcohol addition and filtration gave 1*H*-isochromene-1,4(3*H*)-dione**44** (yield: 75.0%). To the solution of **6a** in ethyl acetate with a few drop of dimethylformamide (DMF, as catalyast), oxalyl chloride ($COCl_2$) was added, heated to 55^{o}C till clear solution. It was later taken up for reduction using Pd/C in H_2 atmosphere under pressure with suitable solvents to get *trans*-4-(4-chloro-phenyl)cyclohexanecarbaldehyde **45a**. Isobutyl-amine (IBA)

mediated condensation of **44** and **45a** in AcOH at 40°C for 3 hr, followed by water addition, filtration and cake wash by the solvent mixture (isopropyl alcohol&water) gave (3*Z*)-3-{[*trans*-4-(4-chlorophenyl)cyclohexyl]methy-lid-ene}-1*H*-isochromene-1,4(3*H*)-dione**46a** (yield: 76-78%). Impact of sodium methoxide (NaOMe) in methanol on **46** for 18-20hr at 20°C, followed by dilute AcOH addition and filtration gave **1a** (yield: 91%) (**Scheme 11a**). The solution of methyl *trans*-4-(4-chlorophenyl)-cyclohexanecarboxylate **47a** in dichloromethane at -78°C in an inert atmosphere, was treated with di-iso-butyl ammonium hydride (DIBAL). After the reaction completion, methanol addition, acidification, extraction, water wash, solvent evaporation, ethyl acetate addition and filtration gave **45a**. Ammonium acetate (NH_4OAc) driven coupling of **44** and **45a** in AcOH at 70°C for 2 hr, followed by water addition, filtration, cake wash by *tert*-butyl methyl ether (TBME) gave **46a**. Further, NaOMe impact on **46a** in methanol gave **1a** (**Scheme 11b**). Lithium aluminum hydride ($LiAlH_4$) mediated reduction of **47a** in THF at 0°C for about 1 hr, followed by acidification, ethyl acetate addition, extraction, water wash and solvent evaporation gave [*trans*-4-(4-chlorophenyl)cyclo-hexyl]methanol **48a**, which was not isolated, instead taken to dimethyl sulfoxide (DMSo) for next step. It was taken in DMSo and treated with TEA, pyridine sulfur trioxide (pyr-SO_3) at 0-20°C for 2 hr, followed by ethyl acetate addition, acidification, extraction and solvent evaporation to get **45a**, which was not isolated, instead taken to AcOH for next step. Morpholine mediated condensation of **44** and **45a** in AcOH at 40°C for 4 hr, followed by water addition, filtration and cake wash by TBME gave **46a**. It was converted to **1a** under the influence of NaOMe or dimethylamino-pyridine (DMAP) in good yield and purity through phosphoric acid (H_3PO_4) or AcOH neutralization (**Scheme 11c**). The disclosed process does not involve the column chromatography for the isolation of intermediates or products. Hence it can be adopted with minor modifications for the large scale manufacturing of the drug.



Scheme 12. Synthesis of **1a** from **6**(**a**,**b**) and **7**.

In 2011/2012, Vyas et al. [32, 33] had reported the use of an aqueous bi-phase solvent system mediated coupling of **6**(**a**,**b**) and **7** under the influence of $AgNO_3$ and $(NH_4)_2S_2O_8$. It was followed by four different work-up procedures were followed to isolate **8a** (yield: 16-19%). An alkali mediated hydrolysis of **8** in aqueous methanol and its acidification gave crude **1a** (95-97%). A few different recrystallization methods were followed to obtain **1a** by the use of solvents such as isopropyl alcohol (yield: 84.0%), acetone (yield: 71.0%), acetonitrile (yield: 80.0%), ethyl acetate (yield: 70-75%) etc. (**Scheme 12**). The disclosed process reports a known pathway to condense **6**(**a**,**b**) and **7**, followed by the solvent driven pathway for the isolation of intermediates and the product with good yield and better purity. The disclosed process was empowered with optimization initiatives, hence, the synthetic pathway will suite for large scale manufacturing of the drug.

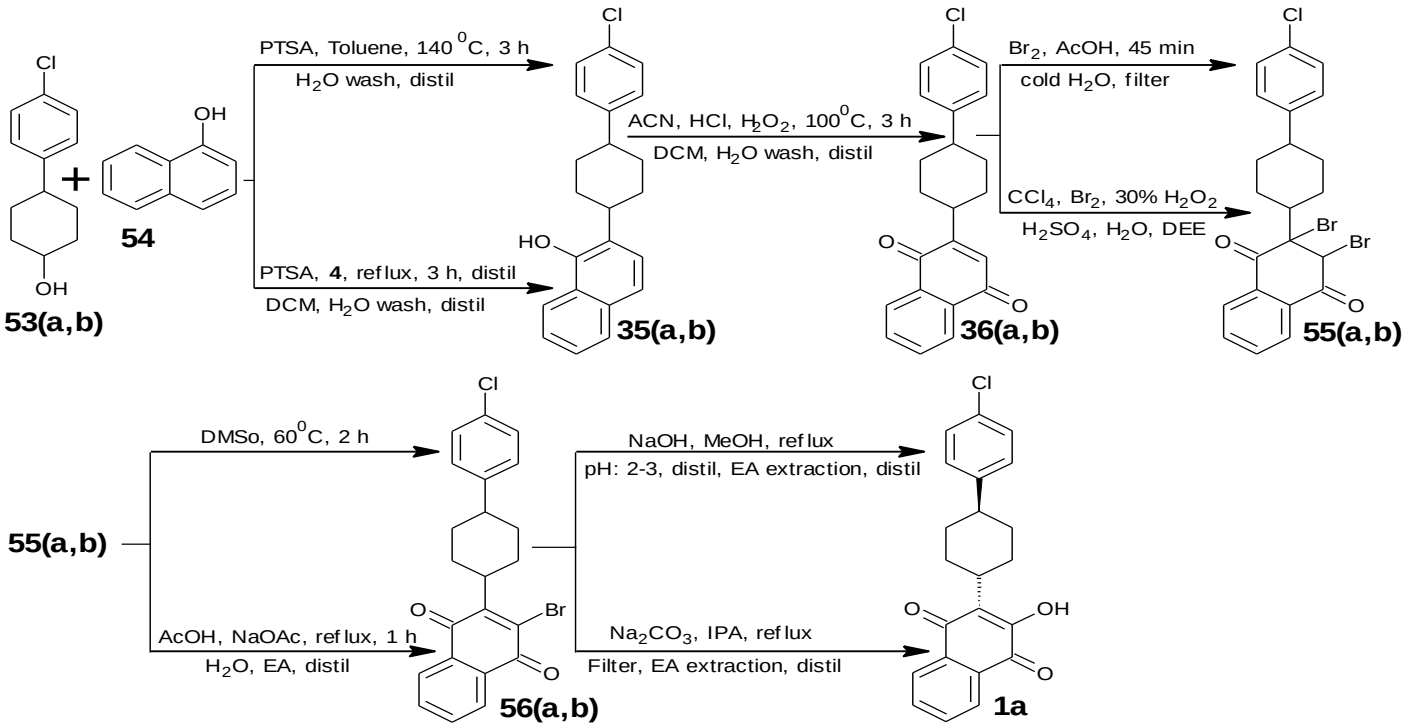


Scheme 13: Synthesis of **1** from **6a**, **41**, **42** and **47a**

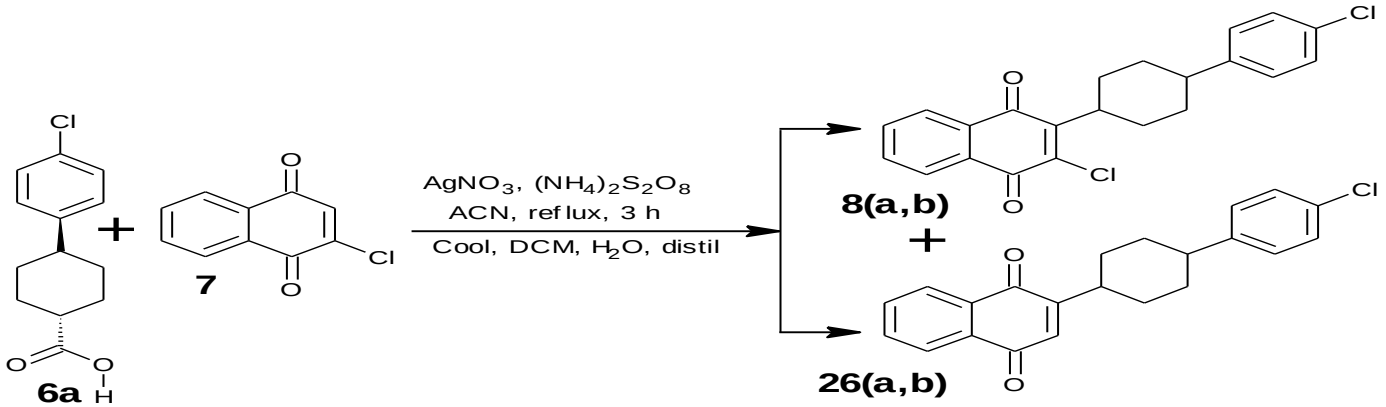
Inspired by the initiatives of Parikh et al. during 1967 [34], Rylander et al. [35] during 1967, and Barcia et al. [36] during 2002, a readily available and commercially affordable **41** was used for the synthesis of **1a** in 2012 by Britton et al. [37]. It was treated with **42** in the presence of TEA at 80^{o}C for 10 hr, followed by quenching to dilute HCl, filtration and water wash to get **43** (yield: 67.0%). It was reacted with 5.5 M HBr and Br_2 in AcOH at 30^{o}C for 3 hr, followed by water addition, reflux for 3 hr, extraction by **4** (as solvent), solvent evaporation, isopropyl alcohol addition and filtration gave **44** (yield: 73.0%). The borohydride driven reduction of **6a** or **47a** in THF under reflux for 2 hr, followed by quenching to aqueous HCl, ethaylacetate extraction, water wash and solvent evaporation gave [*trans*-4-(4-chlorophenyl)cyclo-hexyl]meth-anol**48a** (yield: 90-96%). Impact of TEA, DMSo and py-SO_3 on **48a** at RT for 1 hr, followed by the addition of water, ethyl acetate, extraction, water/brine wash and solvent evaporation gave **45a** (yield: 95.0%). NH_4OAc mediated condensation of **44** and **45a** in AcOH at 60^{o}C for 1.5 hr, followed by cooling to RT, water addition, filtration and cake wash by the mixture of water and TBME gave **46a** (yield: 72.0%). NaOMe in methanol was used to convert **46a** to **1a** at 20^{o}C for 18-20 hr, followed by acidification with aqueous AcOH, methanol addition and filtration gave **1a** (yield: 85.8%). Di-isobuty-laluminium hydride (DIBAH) mediated reaction of **6a** or **47a** in dichloromethane at -78^{o}C for 1.5 hr, followed by methanol addition, acidification by HCl solution, water wash, ethyl acetate addition and solvent evaporation gave **45a**, which was not isolated. It was dissolved in AcOH and condensed with **44** at 60^{o}C for 2 hr, followed by water addition, filtration and cake wash by TBME gave **46a** (yield: 68%). The addition of $COCl_2$ to the solution of **6a** in ethyl acetate with a few catalytic drops of DMF at 55^{o}C until clear solution, followed by the addition of quinaldine at 20^{o}C, hydrogenation in presence of Pd/C with H_2, filtration and ethyl acetate addition gave **45a** or *trans*-4-(4-chlorophenyl)cyclohex-anecarbonylchloride**49a**, which are not isolated. To the solution of **45a** or **49a** in ethyl acetate, **44** in AcOH and IBA were added at 38^{o}C, followed by filtration and cake wash by isopropyl alcohol gave **46a** (yield: 81.0%). A mixture of **46a** and dimethylaminopyridine (DMAP) in toluene and methanol was heated to 67^{o}C for 4 hr, followed by HCl addition, water wash, solvent evaporation, methanol addition and filtration gave the *trans*-isomer of methyl-2-{3-[4-(4-chlorophenyl)cyclo-hexyl]-2-oxopropanoyl}be-nzoate **50a** (yield: 77%). NaOMe impact on **50a** in methanol gave **1a** (yield: 86%). Similarly, the mixture of **46a** and DMAP in methanol was refluxed for 25-26 hr, followed by solvent evaporation, addition of TBME, overnight stand-off and filtration gave *trans*-isomer of 3-{[4-(4-chlorophenyl)cyclo-hexyl] acetyl}-3-(methyloxy)-2-benzofuran-1(3H) -one **51a** (yield: 14.7%) along with the by-product 3-(2-((1r,4r)-4-(4-chlorophenyl)cyclohex-yl)ace-tyl) - 3 - hydroxyisobenzofuran - 1 (3H) - one **52a** (**Scheme 13**). The disclosed process was simple and involves the use of cheap raw materials/ reagents to prepare the product and key inter-mediates. The process avoids the silver mediated pathway and epimerization consequences to isolate **1**. The reported experiments were demonstrated in a substantial high scale including the Rosenmund method, disclosed by Iosub & others in 2018 [38] along with the details on impurity prevention and its elimination. With these consequences, the process fits well for large scale manufacturing of the drug.

In 2013, Dong et al. [39] had reported the PTSA mediated condensation of 4-(4-chlorophenyl) cyclohexanol **53**(**a**,**b**) and naphtha-ene-1-ol **54** in the presence and absence of toluene to get **35**. The impact of H_2O_2 and HCl in acetonitrile on **35**(**a**,**b**), followed by chloroform extraction, water wash and solvent evaporation gave **36**(**a**,**b**). It was converted to 2,3-dibromo-2-[4-(4-chlorophenyl)cyclohexyl]-2,3-dihydronaphthalene-1,4-dione **55**(**a**,**b**), either by the use of Br_2 in AcOH or Br_2, 30% H_2O_2 and H_2SO_4 in carbontetrachloride. Addition of DMSo to **55**(**a**,**b**) and heating to 60^{o}C for 2 hr, followed by water washing and precipitation gave 2-bromo-3-[4-(4-chlorophenyl)-cyclohexyl]-naphthalene-1,4 dione **56**(**a**,**b**). Similarly, NaOAc in AcOH impact on **55**(**a**,**b**) under reflux for 1 hr, followed by water addition, ethyl acetate extraction and solvent

evaporation gave **56**(**a**,**b**). It was refluxed with NaOH in MeOH, followed by acidification to pH: 2-3, solvent evaporation, extraction to ethyl acetate and solvent evaporation gave **1a**. Similarly, **56**(**a**,**b**) was refluxed with sodium carbonate (Na_2CO_3) in isopropyl alcohol, followed by filtration, distillation, ethyl acetate extraction and solvent evaporation gave **1a** (**Scheme 14**). The disclosed process uses commercially affordable and abundant key raw materials/reagents and also avoids the use of expensive silver to provide a good purity and (un-disclosed) yield. Hence, the process suits well for scalability of the drug with minor modifications.



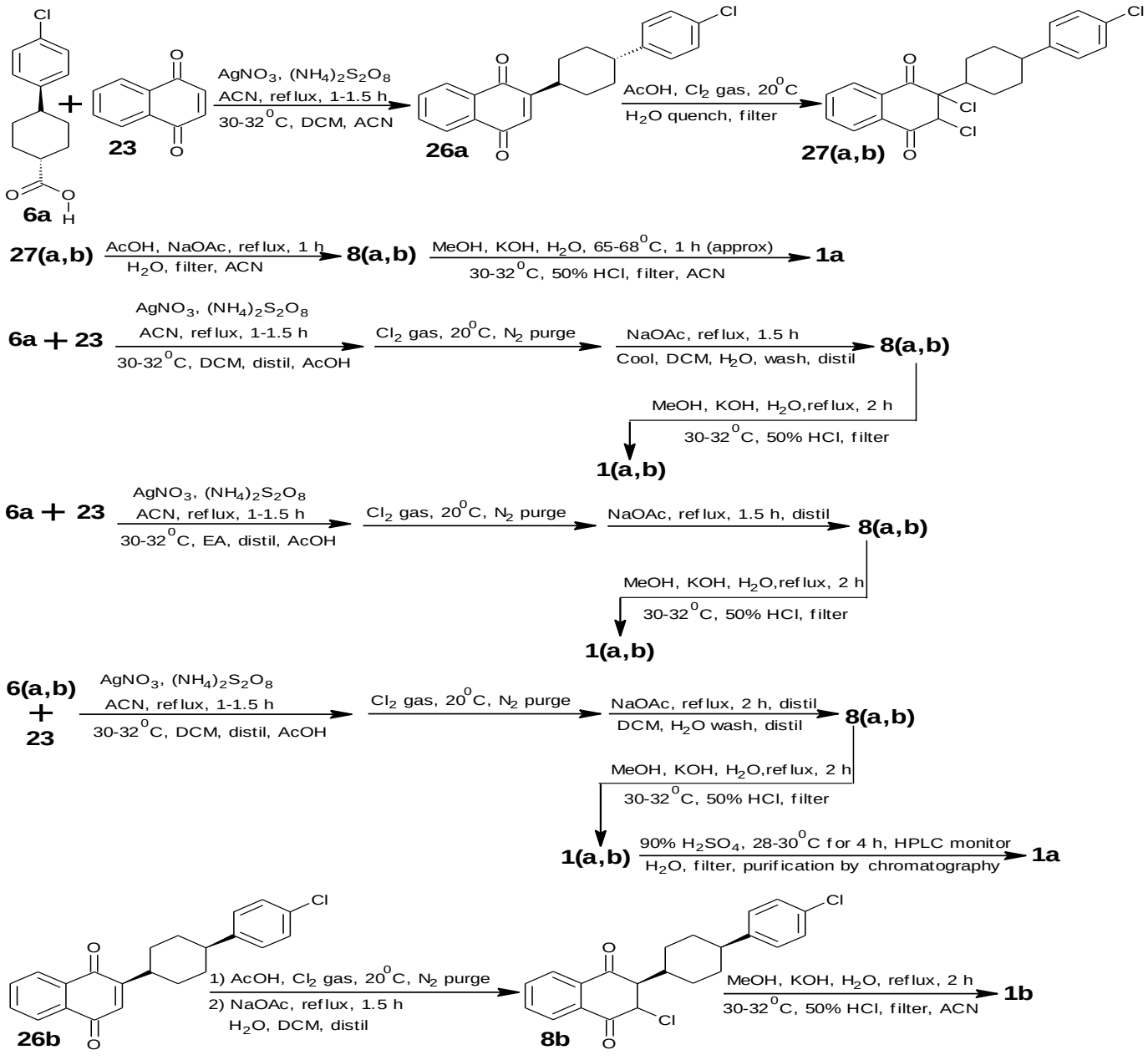
Scheme 14: Synthesis of **1a** from **53**(**a**,**b**) and **54**



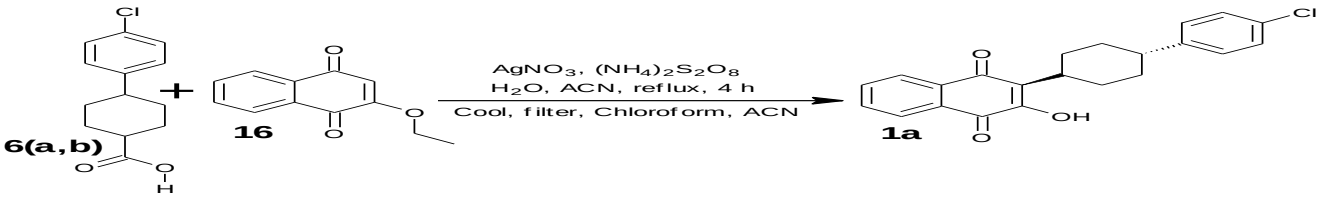
Scheme 15a: Synthesis of **8**(**a**,**b**) from **6a** and **7**

In 2014, Dike et al. [41] had illustrated the silver catalyzed and persulfate driven condensation of **6a** and **7** in acetonitrile under reflux for 3 hr, followed by extraction to dichloromethane, water wash and solvent evaporation to get the surprising combined output of **8**(**a,b**) and **26**(**a,b**). It was evident by the results of HPLC and mass spectral analysis of the obtained yellowish brown residue (**Scheme 15a**). A similar synthetic pathway was adopted for the condensation of **6a** and **23**, followed by dichloromethane addition, water wash, distillation, acetonitrile slurry (twice) and filtration gave **26a** (yield: 20.8%) with a m.p. of 147-149°C. Glacial AcOH was added to **26a** and passed Cl_2 gas at 20°C,

followed by filtration and bed wash to neutral pH gave **27**(**a**,**b**) (yield: 85.9%). It was suspended in glacial AcOH and anhydrous NaOAc was introduced and refluxed for 1 hr, followed by water addition, filtration and recrystallization in acetonitrile gave **8**(**a**,**b**) (yield: 89%) with a m.p. of 185-187ºC. An alkali (KOH solution) driven hydrolysis of **8**(**a**,**b**) in methanol, followed by acidification, filtration and recrystallization in acetonitrile gave **1a** (yield: 85%) with a m.p. of 219-221ºC. Two distinct experiments were done to isolate **1**(**a**,**b**) (yield: 81.3% and 84.6%) through a one pot process starting from **6a** and **23,** with minor changes in work up pathway. **1**(**a**,**b**) was successfully epimerized (in 2008, Zhu & others) [40] under the influence of 90% H_2SO_4 at 28-30ºC for 4 hr, followed by water quench and chromatographic purification to get **1a** (yield: 42.0%). A similar synthetic strategy was employed to condense **6**(**a**,**b**)with **23** to isolate **1**(**a**,**b**), followed by epimerization and column chromatography to get **1a** (yield: 41%). An attempt to was made with success to convert **26b** to **8b** and then to **1b** (yield: 65%) by chlorination, hydrolysis, acidifcation and recrystallization in acetonitrile (**Scheme 15b**). Disclosed process was executed in reasonably large scale with good yield and purity. The multi-step process and the use of column chromatography to isolate **1a**, forms a certain bottle neck for large scale manufacturing of the drug.

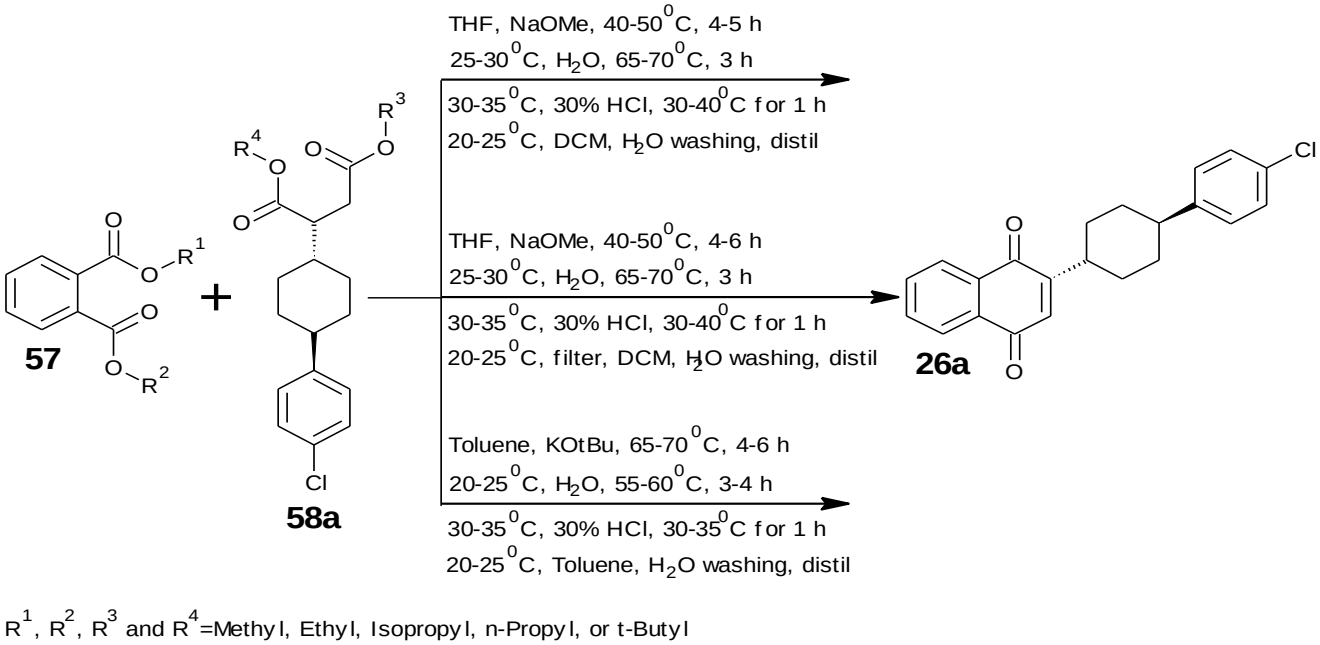


Scheme 15b: Synthesis of **1a** and **1b** from **6a**/**6**(**a**,**b**) and **23**

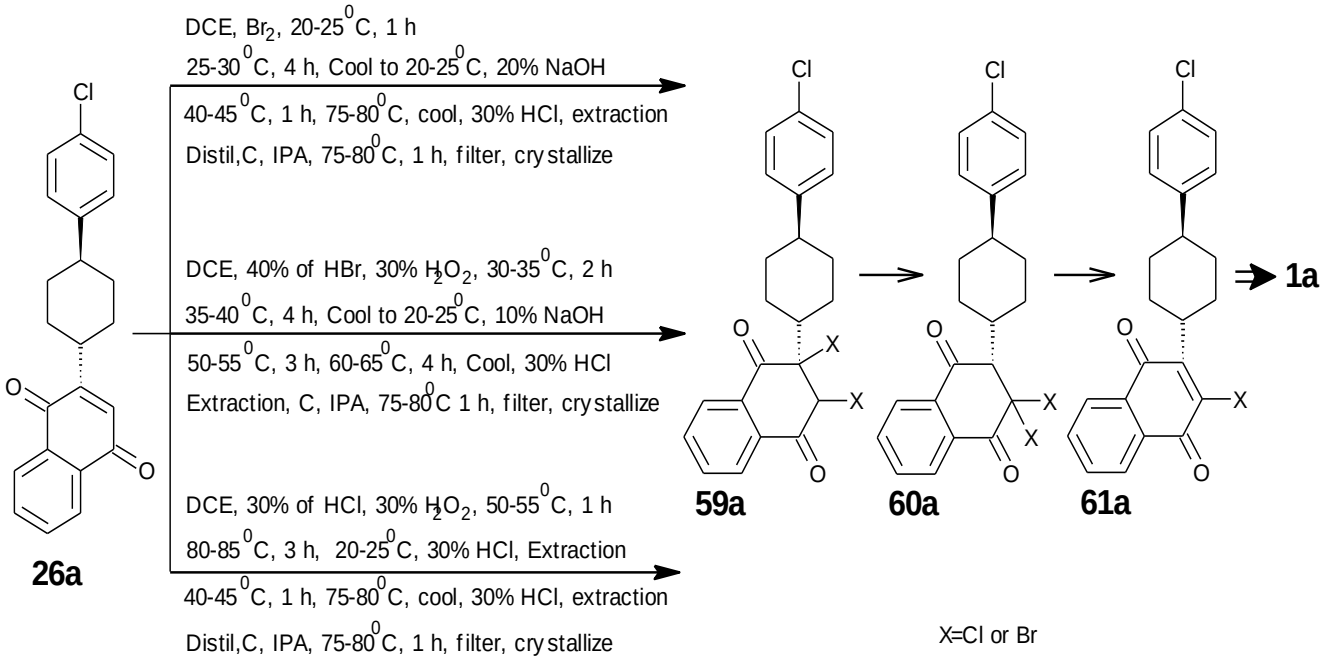


Scheme 16. Synthesis of **1a** from **6**(**a**,**b**) and **16**

In 2016, Zhang [42] had demonstrated a simple one-step process for the synthesis of **1a** by the condensation of **6**(**a**,**b**) and **16** in acetonitrile and water under the mediation of silver and persulfate at reflux condition for 4 hr. After the reaction completion, it was cooled, filtered, solid was taken to chloroform, filtered to remove the insoluble and recrystallized in acetonitrile to get **1a** (**Scheme 16**). There is no mention on the process yield and recovery/reuse of silver salt. Based on the one-step pathway and the commercial viability of the key raw materials, the disclosed process would suite well for large scale manufacturing of the drug.



Scheme 17a. Synthesis of **26a** from **57** and **58a**



Scheme 17b. Synthesis of **1a** from **26a**

In 2018, Cui et al. [43] had reported the NaOMe mediated condensation of the phthalate derivative **57** and cyclohexyl succinate derivative **58a** in THF at 40-45^{o}C for 4-5 hr. It was followed by cooling, water addition, heating to 65-70^{o}C for 3 hr, cooling, acidification by HCl, dichloromethane addition, extraction, water wash and solvent evaporation gave **26a** (yield: 91.3%). A similar reaction pathway with minor changes gave **26a** (yield: 66.7%) and the use KOtBu in toluene to condense **57** with diethyl cyclohexyl succinate derivative **58a** gave **26a** (yield: 92.2%) (**Scheme 17a**). Further, it was subjected to halogenation, de-halogenation, hydrolysis, acidification and recrystallization in isopropyl alcohol to get **1a**. Meanwhile, the reaction would generate di-halo intermediates (**59a** and **60a**), mono-halo inter-mediate (**61a**) and they were not isolated. The halogenation was done by the use of either Br_2, HBr or HCl in dichloroethane (DCE) as solvent and hydrolysis by NaOH solution. An activated charcoal (C) driven de-colorization was done in isopropyl alcohol to get the crystals of **1a** (yield: 80-90%, as per 4 distinct experiments) (**Scheme 17b**). The disclosed process has some advantages like, the raw materials used are relatively cheap and abundant. Further, it avoids the use of expensive silver nitrate, instead it propels by use of cheaper and commonly available reagents and solvents. The mild reaction conditions, high reaction selectivity, good yield and purity, would make this invention to suite for large scale manufacturing of the drug.

A brief outline of the entire review work has been tabulated in **Table 2**, with the scheme number (S. N.), steps involved in the inventions and the key remarks on the process. Various raw materials, reagents and solvents were used for the synthesis of **1a** in one-step, two-step and multi-step process pathways. Among them, eleven disclosures had the mediation of silver salt for the synthesis of **1a**, remaining six disclosures could able to achieve the synthesis by the use of reagents other than silver salt. Stereo specific intermediates and product along with their poor solubility in water and solvents, had allowed the possibility to go for the process development initiatives and contribute to the synthesis of drug in large scale. A minimum process steps, mild reaction conditions, use of readily available reagents/raw materials/solvents, high atom economy, least effluents etc. are the key aspects to be focused for effective drug comer-cialization. These vital and critical aspects itself would form a bottle neck for the large scale manufacturing of **1a** in most disclosed routes. In this regard, around twelve synthetic disclosures were peripherally found to suite for scalability (with minor modifications), remaining 5 processes would require major modifications to go for scalability. Meantime, this review work will provide an opportunity for researchers to venture further to design a scalable process for **1a** in accordance to green chemistry principles. Recently a review work was published by Khan and others [44] in 2023 had comprehensively covered the details on the synthesis and applications of naphthaquinone-based drugs. More importantly, the work had wide view coverage of on the synthesis of numerous drugs including **1a** in brief. Under the similar context, a review work by Spyroudis [15] in 2000 had aimed broadly at the details on the synthesis and reactivity of hydroxyquinones. Our present venture is specific towards the synthetic aspects of drug **1a**, evolved by the thorough examination of the prior art disclosures with a progressive methodological flourish of **1a**.

Table 2: A brief outline of the review work for process steps involved and remarks on scalability.

S. N.	Process pathway	Silver salt mediation	Scalability
1	Multi-step	Y	N
2	Multi-step	Y	N
3	Two-step	Y	Y
4	One-step	Y	Y
5	Multi-step	Y	N
6	Multi-step	N	Y
7	Two-step	Y	Y
8	Two-step	Y	Y
9	Multi-step	Y	Y
10	Multi-step	N	N
11	Multi-step	N	Y
12	Two-step	Y	Y
13	Multi-step	N	Y
14	Multi-step	N	Y
15	Multi-step	Y	N
16	One-step	Y	Y
17	Multi-step	N	Y
Y = Yes, N = No			

Conclusion: Silver centric synthesis of **1a** has been the major process backbone, as per prior arts. So that, avoiding the use of $AgNO_3$ would reduce the overall process cost to about 60.0%. Hence, a few inventions were emerged by avoiding it for the synthesis of **1a**. Another ventured option in line to the context was the recovery of silver salt and its reuse for the reaction along with recovered solvents. A stiff process development studies were performed in a few works to achieve relatively better atom economy, purity and effluent reduction.

In this review, we have considered the work of global researchers towards the synthesis of **1a** by covering all process details progressively disclosed by them till date. In line to it, around seventeen reaction schemes were drawn for the elaborate understanding of the pathway followed for the synthesis of **1a**. This study will provide a firm template to design a new synthetic route or re-work on the existing routes to achieve the ideologies of green chemistry alongside commercialization of **1a**.

Acknowledgements: The authors thank the governing officials of SDM Educational Society (Ujire) and Alkem Laboratories Limited (Mumbai), for rendering us the motivation and immense support to complete the present review work on **1a**.
Author contribution: Both the authors had contributed equally.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification, and double publication or submission have completely been observed by authors.

References

1. Hughes WT (1995) The role of atovaquone tablets in treating pneumocystis carinii pneumonia. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology. 8 (3): 247-252. doi.org/10.1097/00042560-199503010-00005
2. McKeage K, Scott L (2003) Atovaquone/proguanil: a review of its use for the prophylaxis of Plasmodium falciparum malaria. Drugs. 63 (6): 597-623. doi: 10.2165/00003495-200363060-00006
3. Shanks GD, Gordon DM, Klotz FW, Aleman GM, Oloo AJ, Sadie D, Scott TR (1998) Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for Plasmodium falciparum malaria. Clinical Infectious Diseases. 27 (3): 494-499. doi.org/10.1086/514710
4. Sukwa TY, Mulenga M, Chisdaka N, Roskell NS, Scott TR (1999) A randomized, double-blind, placebo-controlled field trial to determine the efficacy and safety of Malarone (atovaquone/proguanil) for the prophylaxis of malaria in Zambia. The American Journal of Tropical Medicine and Hygiene. 60 (4): 521-525. doi.org/10.4269/ajtmh.1999.60.521
5. Staines HM, Burrow R, Teo BHY, ChisSter I, Kremsner PG, Krishna S (2018) Clinical implications of Plasmodium resistance to atovaquone/proguanil: a systematic review and meta-analysis. The Journal of Antimicrobial Chemotherapy. 73 (3): 581-595. doi.org/10.1093/jac/dkx431
6. Xiang M, Kim H, Ho VT, Walker SR, Bar-Natan M, Anahtar M, Liu S, Toniolo PA, Kroll Y, Jones N, Giaccone ZT, Heppler LN, Ye DQ, Marineau JJ, Shaw D, Bradner JE, Blonquist T, Neuberg D, Hetz C, Frank DA (2016) Gene expression-based discovery of atovaquone as a STAT3 inhibitor and anticancer agent. Blood. 128 (14): 1845-1853. doi.org/10.1182/blood-2015-07-660506
7. Carter-Timofte ME, Arulanandam R, Kurmasheva N, Fu K, Laroche G, Taha Z, van der Horst D, Cassin L, van der Sluis RM, Palermo E, Di Carlo D, Jacobs D, Maznyi G, Azad T, Singaravelu R, Ren F, Hansen AL, Idorn M, Holm CK, Olagnier D (2021) Antiviral potential of the antimicrobial drug atovaquone against SARS-CoV-2 and emerging variants of concern. ACS Infectious Diseases. 7 (11): 3034-3051. doi.org/10.1021/acsinfecdis.1c00278
8. Sykes JE, Papich MG (2014) Antiprotozoal Drugs. In: Canine and Feline Infectious Diseases, Elsevier, Saunders. 97-104. ISBN: 9780323241946
9. Krause PJ, Lepore T, Sikand VK, Gadbaw J, Jr Burke G, Telford SR, 3rd Brassard P, Pearl D, Azlanzadeh J, Christianson D, McGrath D, Spielman A (2000) Atovaquone and azithromycin for the treatment of babesiosis. The New England Journal of Medicine. 343 (20): 1454-1458. doi.org/10.1056/NEJM 200011163432004
10. Baggish AL, Hill DR (2002) Antiparasitic agent atovaquone. Antimicrobial Agents and Chemotherapy. 46 (5): 1163-1173. doi.org/10.1128/AAC.46.5.1163-1173.2002

11. Clark HL, Minns MS, Sun Y, de Jesus T, Ghannoum MG, Pearlman E (2018) Atovaquone impairs growth of Aspergillus and Fusarium keratitis isolates by modulating mitochondrial function and zinc homeostasis. Investigative Ophthalmology and Visual Science. 59 (3): 1589-1598. doi.org/10.1167 /iovs.17-22585
12. Futuro DO, Ferreira PG, Nicoletti CD, Borba-Santos LP, Silva FCDA, Rozental S, Ferreira VF (2018) The antifungal activity of naphthoquinones: An integrative review. Anais Da Academia Brasileira de Ciencias. 90 (1S 2): 1187-1214. doi.org/10.1590/0001-3765201820170815
13. Sanjay SS, Shashiprabha, Shridhara K, Nagarajan K (2022) Synthesis, structural elucidation and reaction optimization studies of a novel prodrug of Atovaquone. Journal of Chemical Sciences (Bangalore, India). 134 (1). doi.org/10.1007/s12039-022-02029-1
14. Kasturi TR, Arunachalam T (1966) A general method of preparation of substituted 2-hydroxy-1.4-Quinones. Canadian Journal of Chemistry. 44 (9): 1086-1089. doi.org/10.1139/v66-161
15. Spyroudis S (2000) Hydroxyquinones: Synthesis and reactivity. Molecules (Basel, Switzerland). 5 (12): 1291-1330. doi.org/10.3390/51201291
16. Paengsri W, Promsawan N, Baramee A (2021) Synthesis and evaluation of 2-hydroxy-1,4-naphtho-quinone derivatives as potent antimalarial agents. Chemical and Pharmaceutical Bulletin. 69 (3): 253-257. doi.org/10.1248/ cpb.c20-00770
17. Hudson AT, Randall W (1991) Naphthoquinone derivatives, US Patent 5053432A, filed on December 26, 1989.
18. Hudson AT, Latter V (1994) Medicaments, EP Patent 0580185 A1, filed on August 15, 1989.
19. Coppa F, Fontana F, Lazzarini E, Minisci F (1992) A new selective method for the homolytic alkylation and carboxylation of quinones by monoesters of oxalic acid. Chemistry Letters. 21 (7): 1299-1302. doi.org/10.1246/ cl.1992.1299
20. Williams DR, Clark MP (1998) Synthesis of atovaquone. Tetrahedron Letters. 39 (42): 7629-7632. doi.org/10.1016 /s0040-4039(98)01691-8
21. Verma SS, Patel DJ, Dwivedi SD (2008) Process for preparation of Atovaquone and the conversion of cis-isomer to trans-isomer, WO Patent 2008122988 A1, filed on April 3, 2008.
22. Wang Y, Liao J, Li Q, Liu Q (2008) Process for preparation of Atovaquone, CN Patent 101265171 A, filed on April 30, 2008.
23. Antonio N, Mara S, Annibale S, Stefan M (2010) Process for the preparation of trans-2,3-disubstituted naphthoquinones, US Patent 7842840 B2, filed on May 6, 2008.
24. Zhu F, Qiao H, Bekhazi M (2010) Process for preparation of Atovaquone via coupling of 2-thioxopyridin-1(2H)-yl 4-(4-chlorophenyl)cyclohexane with 1,4-naphthoquinone, WO Patent 2010001379 A1, filed on June 30, 2008.
25. Gui H, Zhou Q, Hu X (2010) A process for preparing Atovaquone from 4-(4-chlorophenyl)-cyclohexane-carboxylic acid and 2-chloro-1,4-naphthalenedione, CN Patent 101774901 A, filed on Jan 9, 2009.
26. Saralaya SS, Shashikumar HS, Shashiprabha, Kanakamajalu S, Ranganathan KR, Veeraswamy A, Govindaraju J, Kothapalli SR, Nagarajan K (2012) Preparation of naphthoquinone compounds using 2,3-dihalonaphthoquinone, US Patent 8283499 B2, filed on March 6, 2009.
27. Saralaya SS, Shashiprabha, Kanakamajalu S, Nagarajan K, Ranganathan KR (2022) A systematic study towards the synthesis, isolation, and recrystallization of atovaquone, an antimalarial drug: A sustainable synthetic pathway. Mapana Journal of Sciences. 21 (1): 19-37. doi.org/10.12723/mjs.60.2
28. Saralaya SS, Shashiprabha, Kanakamajalu S, Nagarajan K, Ranganathan KR (2022) A novel and sustainable method for the synthesis of 2-chloro-3-[trans-4-(4-chlorophenyl) cyclohexyl]-1,4-naphtho-quinone, accomplished by systematic process development studies - Trans-Cl synthesis, Mapana Journal of Sciences. 21 (3): 1-19. doi.org/10.12723/mjs.62.0
29. Kumar A, Singh D, Mathur P, Kore SS, Buchude VS (2010) A new process for preparation of Atovaquone and novel intermediates thereof, US Patent 7847127 B2, filed on October 21, 2009.
30. Roy KBN, Singh GP, Lathi PS, Agrawal MK, Mitra R, Trivedi A (2012) A process for the preparation of Atovaquone, WO Patent 2012153162 A1, filed on June 28, 2011.
31. Dwyer AN, Gordon A, Urquhart M (2012) Novel process for preparation of Atovaquone and intermediates thereof, WO Patent 2012080243 A2, filed on December 13, 2011.
32. Vyas JR, Yadav RR, Bhimani AS (2013) Novel process for selective isolation and purification of 2-[4-(4-chlorophenyl) cyclohexyl-3-chloro-l, 4-naphthoquinone and Atovaquone, WO Patent 2013098832 A2, filed on September 7, 2012.
33. Vyas JR, Yadav RR, Bhimani AS (2011) Novel purification method for 2-chloro-3-[4-(4-chlorophenyl) cyclohexyl]-1,4-naphthoquinone and Atovaquone, IN Patent 2011MU02505 A, filed on September 8, 2011.
34. Parikh JR, Doering WVE (1967) Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide. Journal of the American Chemical Society. 89 (21): 5505-5507. doi.org/10.1021/ja00997a067
35. Rylander PN (1967) Hydrogenation of aldehydes. In: Catalytic hydrogenation over platinum metals, Elsevier, Academic Press, pp. 238-257. ISBN: 9780323145862

36. Barcia JC, Cruces J, Estevez JC, Estevez RJ, Castedo L (2002) Palladiumcatalyzed synthesis of o- acetylbenzoic acids: A new, efficient general route to 2hydroxy3-phenyl-1,4naphthoquinones and indolo [2,3b]naphthalene 6,11diones. ChemInform. 33 (42): 109-109. doi.org/10.1002/chin.200242109
37. Britton H, Catterick D, Dwyer AN, Gordon AH, Leach SG, McCormick C, Mountain CE, Simpson A, Stevens DR, Urquhart MWJ, Wade CE, Warren J, Wooster NF, Zilliox A (2012) Discovery and development of an efficient process to atovaquone. Organic Process Research and Development. 16 (10): 1607-1617. doi.org/10.1021/ op300165q
38. Iosub AV, Wallentin CJ, Bergman J (2018) Celebrating 100 years of the Rosenmund reaction. Nature Catalysis. 1 (9): 645-648. doi.org/10.1038/s41929-018-0143-0
39. Dong M, Yan B, Guo Q, Dong K, Peng X, Wu M (2014) Benzoquinone, its preparation and application for preparation of Atovaquone, CN Patent 103570520 A, filed on August 21, 2013.
40. Zhu F, Bekhazi M (2011) Process for the epimerization of atovaquone isomer, atovaquone intermediates and mixture thereof, US Patent 0144347 A1, filed on June 30, 2008.
41. Dike SY, Singh D, Thankachen BN, Sharma B, Mathur PK, Kore S, Kumar A (2014) A single-pot synthesis of atovaquone: An antiparasitic drug of choice. Organic Process Research and Development. 18 (5): 618-625. doi.org/10.1021/op500032w
42. Zhang J (2016) Process for the preparation of Atovaquone, CN Patent 105622381 A, filed on November 7, 2014.
43. Cui Q, Wang B, Xu X, Wang Q, Ju L (2020) Method for preparing Atovaquone, CN Patent 110734369 A, filed on July 19, 2018.
44. Khan J, Rani A, Aslam M, Pandey G, Nand PB (2023) A review on the synthesis and application of naphthoquinone-based drugs. Results in Chemistry. 6 (101138): 101138. doi.org/10.1016/j.rechem. 2023.101138